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Original Article

Increased protein arginine methyl transferase 7 expression is correlated with the occurrence and development of endometrial carcinoma

Yuanyuan Chen[1], Binqiao Wang[2], Xiaoxiao Lan[2], Zhiyang Zhou[2], Xueqing Wu[2,3]

[1]Wenzhou People's Hospital, The Third Clinical Institute Affiliated to Wenzhou Medical University, Wenzhou 325000, China; [2]Department of Gynaecology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China; [3]Department of Gynaecology, Shenzhen University General Hospital, Shenzhen 518071, China

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Abstract: *Objective:* The aim of the present study was to investigate protein arginine methyl transferase 7 (PRMT7) expression in endometrial cancer cells and to assess the involvement of PRMT7 in the occurrence and development of endometrial carcinoma. *Methods:* Real-time PCRand immunohistochemistry-SP were performed to determine PRMT7 mRNA and protein expression, respectively, in normal endometrial tissues and endometrial carcinoma tissues. The correlations between PRMT7 protein expression and clinicopathological parameters of patients with endometrial cancer were analyzed retrospectively by comparing the positive rate among different groups. *Results:* PRMT7 expression was higher in stage I/II endometrial cancer tissues than in normal endometrial tissues, but the difference was not statistically significant (P = 0.105). PRMT7 expression was significantly higher in stage III/IV endometrial cancer tissues than in normal endometrial tissues (P<0.001). Moreover, PRMT7 expression was associated with the differentiation degree (P = 0.007), distant metastasis (P = 0.015), and International Federation of Gynecology and Obstetrics (FIGO) stage (P = 0.028) of endometrial cancer but not with the age of patients with endometrial cancer (P = 0.063). *Conclusion:* These results suggest that PRMT7 participates in the occurrence and development of endometrial carcinoma, and is a novel candidate biomarker of endometrial serous carcinoma.

Keywords: PRMT7, endometrial carcinoma, immunohistochemistry, real-time PCR

Introduction

Endometrial carcinoma (EC) is the most prevalent gynecological malignancy worldwide, with an increasing incidence and mortality [1-3]. Most epidemiological studies have classified ECs into the two most common types, types I and II, based on their clinical features and pathogenesis [4]. EC classification is not limited to the association between ECs and estrogen. Molecular classification of ECs has recently gained popularity because conventional EC classification based on histopathological subtypes and grades is unreliable [5-9] and in line with the trends in precision medicine for personalized treatment options. Molecular classification of ECs is promising and reproducible, and further allows for the prediction of clinical outcomes. The Cancer Genome Atlas has identified four genomic subgroups of EC: POLE mutations, microsatellite instability, low copy number, and high copy number [10]. Numerous genetic alterations are associated with the development of ECs, such as those in genes encoding PTEN, β-catenin, K-ras, p53, p16, and Her2/Neu [11-15]. Overexpression of insulin-like growth factor II mRNA-binding protein 3 (IMP3) has also recently emerged as a potential new biomarker of endometrial serous carcinoma [16].

Protein arginine methyl transferases (PRMTs) are a family of enzymes that regulate biological process such as signal transduction, gene regulation, chromatin remodeling, and RNA splicing [17-21] by modifying substrate proteins through arginine methylation after translation. Several studies have shown that aberrant PRMT expression is closely associated with the development of cardiovascular diseases [22], respiratory

system diseases [23], cancers [24], viral infection, and autoimmune diseases [25]. PRMT7 is an important member of the PRMT family, which was initially characterized as a protein that modulates drug sensitivity to DNA-damaging agents in hamster cells [26]. PRMT7 is involved in several biological processes, including RNA splicing regulation [27], DNA damage repair [28], and cell migration and differentiation [29], and regulates cancer cell sensitivity to anticancer drugs [30, 31]. Other PRMTs are also involved in cancer development; for example, overexpression and aberrant splicing of PRMT1 is observed in breast cancer, prostate cancer, lung cancer, colon cancer, bladder cancer, and leukemia [24]. A recent study highlighted the relationship between PRMT7 and cancers, mainly breast cancer. PRMT7 expression is highly aberrant in breast cancer tissues and promotes the invasion and migration of breast cancer cells [32]. However, PRMT7 expression and its clinical significance in EC are unclear.

Therefore, in the present study, we examined changes in PRMT7 mRNA and protein expression in EC tissues and normal endometrial tissues. We further analyzed the correlation between PRMT7 protein expression and clinicopathological parameters to determine whether PRMT7 expression differs among different EC types, which could be exploited for diagnostic purposes.

Materials and methods

Samples

Freshly frozen tissues for performing RNA isolation and real-time polymerase chain reaction (PCR) and paraffin-embedded tissue specimens for performing immunohistochemistry-SP (IHC-SP) were obtained from 52 patients with EC (age, 46-64 years) who underwent primary surgeries at the Department of Gynecology and Obstetrics, First Affiliated Hospital of Wenzhou Medical University, from June 2014 to June 2016. Patients who were initially treated with radiotherapy, chemotherapy, and hormone therapy were excluded from the study. Overall, 52 EC tissues from 37 patients with EC (stage I, 12 patients; stage II, 8 patients; stage III, 10 patients; and stage IV, 7 patients) and 15 control tissues from subjects with a normal endometrium obtained during hysterectomy for treatment of uterine fibroids were confirmed by pathologists. There was no significant difference in the age of the 37 patients with EC and 15 subjects with a normal endometrium (P = 0.075). Clinical stage assessment was performed using the International Federation of Gynecology and Obstetrics (FIGO) system (1989). Tumor differentiation degree and distant metastasis were also evaluated.

RNA isolation and real-time PCR

Total RNA was isolated from the frozen tissues using TRIzol reagent (Life Technologies, USA) according to the manufacturer's instructions. The RNA was reverse-transcribed to cDNA using RR037A (Takara, Japan). *PRMT7* and *GAPDH* mRNA expression was quantified by real-time PCR. Each sample was analyzed in triplicate. Real-time PCR was performed using Power SYBR Green PCR Master Mix (Thermo Scientific, USA) and ABI 7500 (Applied Biosystems, USA), according to the manufacturers' instructions. After PCR, a melting curve was generated for each amplicon to verify its accuracy. Relative expression of the target genes was normalized to that of *GAPDH*, analyzed using the DDC_t method, and expressed as a ratio of the expression level detected in control tissues. The following primer sequences were used for gene amplification: *PRMT7* sense, 5'-GTT CTG GAT CAG TCG GCC C-3'; *PRMT7* antisense, 5'-TCG TCA TCT TCA GAG TCC A-3'; *GAPDH* sense, 5'-AAC GGA TTT GGT CGT ATT GGG-3'; and *GAPDH* antisense, 5'-CCT GGA AGA TGG TGA TGG GAT-3'.

IHC-SP

Antigens in the paraffin-embedded EC specimens were detected by performing IHC-SP, according to the instructions of the kit. The paraffin-embedded tissue sections (5 μm) were dewaxed and rehydrated by filtering twice in dimethylbenzene and graded ethanol. After blocking endogenous peroxidase activity for 10 min and then microwaving for 10 min to induce antigen retrieval, the slides were blocked using 10% goat serum for 15 min at 37°C. Next, the sections were incubated overnight with anti-PRMT7 antibody (dilution, 1:1000; Abcam, UK) in a wet chamber at 4°C, followed by incubation with horseradish peroxidase-conjugated secondary antibody (Sigma, USA) for 30 min at 37°C. PRMT7 expression was visualized using

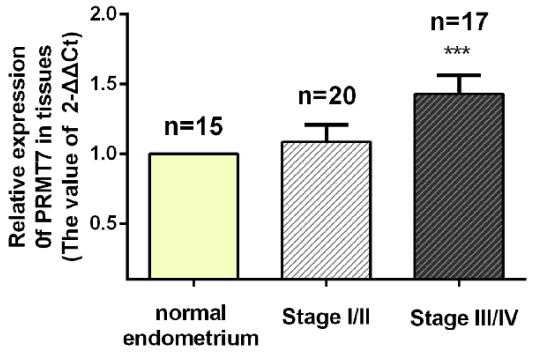

Figure 1. PRMT7 mRNA expression in normal endometrial tissues and stage I/II and III/IV EC tissues; ***P<0.001 compared with normal endometrial tissues.

a diaminobenzidine kit (Zsbio, China), and the nuclei were counterstained with hematoxylin. Sections incubated with equal volumes of phosphate-buffered saline in place of anti-PRMT7 antibody were used as negative controls, and known positive breast cancer tissue sections were used as positive controls. Each section was analyzed in duplicate. Staining intensity was scored from 0 to 3 (0, no staining; 1, weak staining; 2, moderate staining; and 3, strong staining). The staining extent was scored from 0 to 4 based on the percentage of positive cells (0, <5% positive cells; 1, 5-10% positive cells; 2, 11-50% positive cells; 3, 51-75% positive cells; and 4, >75% positive cells). For each slide, the two scores were multiplied to determine PRMT7 expression; a score of ≥6 was graded as positive expression.

Statistical analysis

Differences in PRMT7 mRNA and protein expression in different groups, as detected by real-time PCR and IHC-SP (assessment of composite scores of PRMT7 staining), respectively, were statistically evaluated by one-way analysis of variance with the least significant difference post-hoc test. Association analysis of PRMT7 expression in endometrioid adenocarcinoma tissues and clinicopathological parameters was conducted using the chi-square test. All statistical analyses were performed using SPSS 17.0 and GraphPad Prism 6 software (GraphPad Software Inc., CA, USA). All data are expressed as mean ± SD. $P<0.05$ was considered statistically significant.

Results

PRMT7 mRNA and protein expression levels were significantly increased in stage III/IV EC tissues

PRMT7 mRNA and protein expression in 15 normal endometrial tissues and 37 EC tissues were detected by real-time PCR and IHC-SP, respectively. EC tissues were divided into two groups, namely, stage I/II (20 patients) and stage III/IV (17 patients) EC tissues, using the FIGO system (1989). The *PRMT7* mRNA expression level was significantly higher in stage III/IV EC tissues than in the 15 normal endometrial tissues ($P<0.001$; **Figure 1**). PRMT7 protein expression was mainly observed in the cell membrane and cytoplasm. The PRMT7 protein expression rates were as follows: normal endometrial tissues, 26.7% (4/15); stage I/II EC tissues, 55.0% (11/20); and stage III/IV EC tissues, 88.2% (15/17). The partition chi-squared test result showed that PRMT7 protein expression was significantly different among EC tissues at each stage. In addition, PRMT7 protein expression was significantly higher in stage III/IV EC tissues than in normal endometrial tissues ($P<0.001$; **Figure 2A-C**, **Table 1**), which was consistent with the results of *PRMT7* mRNA expression analysis. However, PRMT7 protein levels in stage I/II EC tissues were not significantly higher than those in normal endometrial tissues ($P>0.05$). The mean composite score of stage III/IV EC tissues was significantly higher than that of control endometrial tissues ($P<0.001$).

Association between PRMT7 protein expression in EC tissues and clinicopathological parameters of patients with EC

Next, we analyzed the association between PRMT7 expression levels and clinicopathological parameters of patients with EC, such as age, tumor differentiation degree, myometrial invasion depth, and FIGO stage, to explore the clinical significance of PRMT7 expression in EC. PRMT7 protein levels were not associated with age ($P>0.05$) but were significantly associated with tumor differentiation degree (**Table 2**). PRMT7 protein levels were higher in EC tissues showing intermediate-to-high differentiation compared to those showing low differentiation ($P<0.05$). Moreover, PRMT7 protein levels were

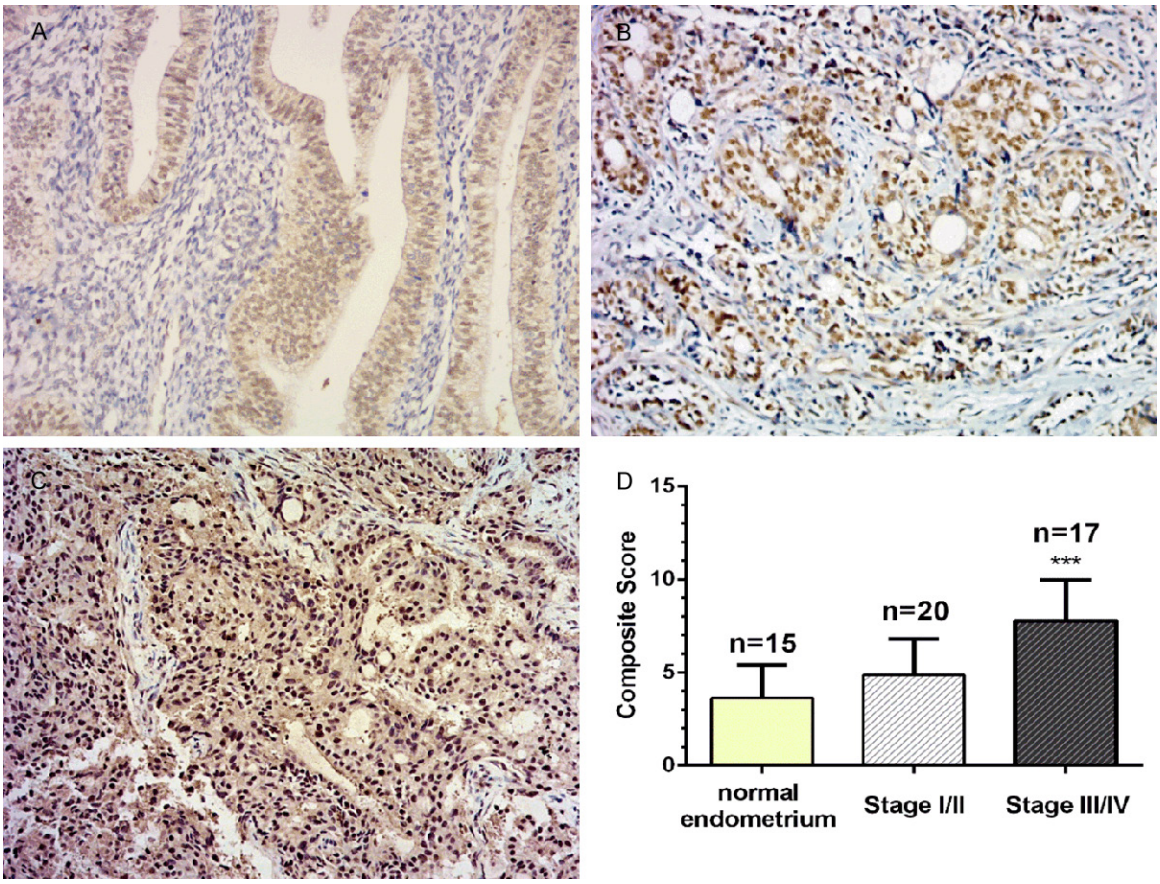

Figure 2. Immunohistochemical staining of PRMT7 protein in normal endometrial tissue and stage I/II and III/IV EC tissues; magnification, ×200. A. Immunostaining of PRMT7 protein in normal endometrial tissue. B. Immunostaining of PRMT7 protein in stage I/II EC tissue. C. Immunostaining of PRMT7 protein in stage III/IV EC tissue. D. Assessment of composite scores of PRMT7 staining for each tissue examined. The mean composite score (intensity × distribution) for normal endometrial tissues, stage I/II EC tissues, and stage III/IV EC tissues, ***P<0.001 compared with normal endometrial tissues.

significantly associated with distant metastasis, with significantly higher PRMT7 protein levels observed in EC tissues showing distant metastasis than in those showing no distant metastasis (P<0.05). Moreover, PRMT7 protein levels were significantly associated with FIGO stage, with higher PRMT7 protein levels observed in stage III/IV EC tissues than in stage I/II EC tissues (P<0.05). These results suggest that PRMT7 participates in the occurrence and development of EC.

Discussion

Epidemiological studies have divided ECs into types I and II based on their clinical features and pathogenesis [4]. Type I ECs include endometrioid carcinomas that are estrogen-dependent and have a favorable treatment outcome. These tumors constitute approximately 60-85% of all ECs and are typically characterized by a low grade and stage. In contrast, type II ECs are estrogen-independent non-carcinomas that are characterized by a high grade and stage with a poor prognosis, and constitute approximately 10-30% of the ECs occurring in elder post-menopausal women [4, 33-35]. Although these are the two most common clinical presentations of EC, there are still many unanswered questions related to EC clinical diagnosis and treatment decisions. In particular, pathologists have been unable to consistently diagnose ECs with different histotypes and grades, leading to their inconsistent classification [5-9]. Moreover, not all type I ECs are estrogen-dependent, and a small portion of type II ECs are suggested to be estrogen-dependent [36]. Therefore, there is a need for an improved

Table 1. Immunohistochemical staining of PRMT7 protein in normal endometrial tissues and stage I/II and III/IV EC tissues

Groups	n	PRMT7 protein expression		χ^2	*P*-value
		Negative (n, %)	Positive (n, %)		
Normal endometrium tissues	15	11 (73.3)	4 (26.7)	22.059	<0.001
Stage I/II endometrial carcinoma tissues[a]	20	9 (45.0)	11 (55.0)		
Stage III/IV endometrial carcinoma tissues[b,c]	17	2 (11.8)	(88.2)		

[a]Stage I/II endometrial carcinoma tissues vs. normal endometrium tissues, $P = 0.712$. [b]Stage III/IV endometrial carcinoma tissues vs. normal endometrium tissues, *P<0.001*. [c]Stage III/IV endometrial carcinoma tissues vs. stage I/II endometrial carcinoma tissues, *<0.001*.

Table 2. Association analysis of PRMT7 expression in endometrioid adenocarcinoma tissues and clinicopathological parameters

Clinical and pathological features	n	PRMT7 protein expression		χ^2	*P*-values
		Negative (n, %)	Positive (n, %)		
Age					
<55	14	7 (50.0)	7 (50.0)	4.430	0.063
≥55	23	4 (17.4)	19 (82.6)		
Tumor differentiation degree					
Middle-high differentiation	25	11 (44.0)	14 (56.0)	7.514	0.007*
Low differentiation	12	0 (0)	12 (100.0)		
Distant metastasis					
Yes	11	0 (0)	11 (100.0)	6.623	0.015*
No	26	11 (42.3)	15 (57.9)		
FIGO Stage					
I/II	20	9 (45.0)	11 (55.0)	4.859	0.028*
III/IV	17	2 (11.8)	15 (88.2)		

*$P<0.05$.

method of EC classification and risk assessment. Development of molecular markers specific to different histological types of ECs would provide useful adjuncts for the current morphological assessment of endometrial lesions, thus contributing to improved patient care. At present, PTEN, β-catenin, K-ras, p53, p16, Her2/Neu, and IMP3 are known markers of EC development [11, 16].

PRMT7, an important member of the PRMT family, is involved in several biological processes, including RNA splicing regulation [27], DNA damage repair through H2AR3me2s and H4R3me2s [28], and cell migration and differentiation [29], and has been shown to increase cancer cell sensitivity to anticancer drugs [30, 31]. PRMT7 expression has been reported in breast cancer cells [28, 32, 37]. However, PRMT7 expression and its clinical significance in EC have not been reported to date. In the present study, we examined PRMT7 expression in normal endometrial tissues and EC tissues. The results of real-time PCR showed that the *PRMT7* mRNA expression level was significantly higher in stage III/IV EC tissues than in normal endometrial tissues and stage I/II EC tissues (**Figure 1**). The subcellular localization of PRMT7 was determined by performing IHC-SP, which showed that PRMT7 protein was localized in the nucleus and cytoplasm of EC cells, with higher expression in the cytoplasm than in the nucleus. PRMT7 protein expression was significantly higher in stage III/IV EC tissues than in normal endometrial tissues and stage I/II EC tissues (**Figure 2A-C**, **Table 1**). To our knowledge, the present study is the first to show that PRMT7 may participate in the occurrence and development of EC.

High PRMT7 expression in breast cancer cells significantly increases the expression of matrix metalloproteinase 9 (MMP9) and promotes cell invasion. This suggests that PRMT7 upregulation in breast cancer plays a significant role in promoting cancer cell invasion through MMP9 regulation, and indicates that PRMT7 could be a novel and potentially significant biomarker and/or therapeutic target for breast cancer [37]. Aberrantly high PRMT7 expression in breast cancer tissues induces epithelial-mesenchymal transition and promotes the invasion and migration of breast cancer cells [32].

PRMT7 knockdown in MDA-MB-231 breast cancer cells inhibits their migration [28]. Collectively, this evidence proves that PRMT7 is involved in the invasion and migration of tumor cells. In the present study, IHC-SP confirmed significantly higher PRMT7 protein levels in EC tissues with distant metastasis than in EC tissues without distant metastasis, in line with the findings of previous studies. Similar results were obtained for PRMT7 protein expression in EC tissues at different FIGO stages (**Table 2**).

PRMT7 inhibits neuronal cell differentiation by repressing MLL4-dependent gene expression [38]. This may affect maintenance of the stem cell population with potential implications in cancer development. Thus, we further examined whether PRMT7 expression was associated with the degree of differentiation of EC. We found that PRMT7 protein levels were higher in EC tissues showing intermediate-to-high differentiation than in those showing low differentiation (**Table 2**).

In summary, this is the first study to report PRMT7 expression in EC tissues based on both real-time PCR and IHC-SP and to retrospectively analyze the correlation between PRMT7 protein expression and the clinicopathological features of patients with EC. We detected PRMT7 mRNA and protein expression in EC tissues, and found that PRMT7 protein expression was associated with the tumor differentiation degree, distant metastasis, and FIGO stage but not with patient age. Thus, our results suggest that PRMT7 participates in the occurrence and development of EC. However, further studies are needed to determine the detailed mechanisms underlying the regulation of the increased PRMT7 expression in EC tissues.

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Disclosure of conflict of interest

None.

Address correspondence to: Xueqing Wu, Department of Gynaecology, The First Affiliated Hospital of Wenzhou Medical University, No. 2, Fuxue Xiang, Wenzhou 325000, China; Department of Gynaecology, Shenzhen University General Hospital, Shenzhen 518071, China. Tel: +86-577-55578166; Fax: +86-577-55578166; E-mail: wutougao@aliyun.com

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