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Expression of MTA1 in endometriosis and its relationship to the recurrence

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Abstract

Metastasis-associated gene 1 (MTA1) is correlated with prognosis of many tumors. However, little is known about the role of MAT1 in endometriosis and its relationship with the recurrence of endometriosis.

The expression of MTA1 in normal, eutopic and ectopic endometrium was detected by immunohistochemistry and RT-PCR, respectively. The relationship of MTA1 expression with the recurrence of endometriosis was evaluated.

In the normal endometrium, eutopic endometrium and ectopic endometrium, the positive rates of MTA1 expression showed a gradually increasing trend. In addition, the MTA1 expression difference between each two groups was significant ($P < .0125$). However, there was no significant difference between proliferative phase and secretory phase in each group ($P > .05$). In the ectopic endometrium, MTA1 expression in the severe phases (III-IV) was significantly higher than that in mild phases (I-II) ($P < .05$), indicating the expression of MTA1 correlates with r-AFS staging ($P < .05$). Additionally, the MTA1 mRNA level was also closely related to the stages of r-AFS, but not to the proliferative phase or secretory phase of endometrium. Logistic regression analysis showed that r-AFS stage and MTA1 overexpression were risk factors for the recurrence of endometriosis. While, postoperative pregnancy was a protective factor for its relapse.

MTA1 is closely associated with the occurrence and development of Ems. Thus, MTA1 level may be used as a new indicator to predict the progression of endometriosis.

Abbreviations: BMI = body mass index, MTA1 = metastasis-associated gene 1, r-AFS = American Society of Reproductive Endometriosis Staging.

Keywords: endometriosis, immunohistochemistry, metastasis-associated gene 1, recurrence, relationship

1. Introduction

At present, endometriosis remains a worldwide problem. Endometriosis induced dysmenorrhea, infertility, intercourse pain and other symptoms could accompany with patients for up to decades or even a lifetime.[1] Moreover, the symptoms will gradually be aggravated. However, the pathogenesis of endometriosis is not clear at present. The current drugs used for endometriosis treatment are mainly hormones;[2,3] however, these drugs are prone to induce liver damage, osteoporosis and other serious side effects.[4] Thus, the continuous use of these drugs should not exceed 6 months. Besides, after discontinuing medication, endometriosis relapses in the majority of patients.[5] Surgical treatment of endometriosis can remove the lesion and help the recovery of pelvic anatomy structure.[6] However, in patients with mild to moderate endometriosis, infertility and recurrence, the value of surgery is still in controversy.[6] In the meantime, although the combination of surgery and medical treatment may improve the therapeutic effect in a short time, recurrence cannot be avoided.[6] Furthermore, although endometriosis is a benign lesion, it has the tumor-like characteristics.[7] Recently, more and more evidence indicates that the histological characteristics of endometriosis and ovarian endometriosis adenocarcinoma are similar to each other.[8–10] Therefore, the relationship between endometriosis and tumor metastasis genes has attracted much attention.

The tumor metastasis-associated gene (MTA) family is closely related to tumor metastasis. There are 3 main members of the family, including MTA1, MTA2, and MTA3, respectively. However, only the carboxyl terminal of MTA1 contains the SH3 structure, which lays a foundation for its interaction with signaling molecules.[11] MTA1 regulates a variety of transcription factors.[12] MTA1 has 2 phosphorylation sites of tyrosine kinases, 7 phosphorylation sites of casein kinase II, and 9 phosphorylation sites of protein kinase C, which determine its function in cell adhesion and migration.[13] In many endometrial-related diseases, the expression of MAT1 is changed.[14]

Here, in this study, we examined the expression of MTA1 in ectopic endometrium, eutopic endometrium, and normal endometrium, respectively. We also analyzed the factors related with the prognosis and recurrence of endometriosis.

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2. Materials and methods

2.1. Patients and samples

Totally, 100 cases of patients, who received laparoscopic surgery for ovarian endometriosis at Haikou Hospital Affiliated to Xiangya Medical College of Central South University from July 2011 to January 2015, were enrolled in this study. Inclusion criteria: patients with pathologically diagnosed ovarian endometriosis; patients with complete clinical data; patients were followed up for 2 to 5 years; with regular menstrual cycle and menstrual period 28 to 35 days; 6 months before surgery, the patient did not use hormones; patients with normal urine routine, vaginal discharge, and blood glucose; mycoplasma, chlamydia, thinprep cytologic test (TCT), and human papillomavirus (HPV) were negative; the estrogen and progesterone levels between patients had no significant difference; and patients with no other underlying diseases. Exclusion criteria: patients with other systemic complications, such as hyperthyroidism or other system tumors.

There were 50 patients with proliferative phase endometriosis and 50 patients with secretory phase endometriosis. According to the American Society of Reproductive Endometriosis Staging (r-AFS), there were 62 cases in stage III to IV and 38 cases in stage I to II. For control, 100 cases with normal endometrium at the same period were selected, including 45 cases at proliferative phase and 55 cases at secretory phase. The average age of subjects was (30.52 ± 8.38) years and the average body weight was 58 ± 9.18 kg. Moreover, the control subjects had normal menstrual cycle and did not receive hormone treatment for 6 months before the hysteroscopy. Additionally, the control subjects were without uterine fibroids and other complications. The clinical data of subjects were listed in Table 1. The ectopic and eutopic endometrium specimens were collected from 100 cases of ovarian endometriosis patients. The normal endometrium specimens were collected from 100 control subjects during hysteroscopy. Prior written and informed consent were obtained from every patient and the study was approved by the ethics review board of Affiliated Haikou Hospital, Xiangya Medical College of Central South University.

2.2. Immunochemistry

The specimens were fixed with 10% neutral formaldehyde, dehydrated, paraffin-embedded and cut into sections. Sections were dewaxed and rehydrated in graded alcohols. After incubation with 0.3% hydrogen peroxide to inactivate endogenous peroxidase activity, antigen retrieval was performed. After washing, the sections were blocked with 10% rabbit serum for 10 minutes at room temperature. Primary antibody of rabbit anti-human anti-MTA1 polyclonal antibody (Cell Signaling Technology, Inc (CST), Danbers, MA) was added and then incubated overnight at 4°C. After washing, the sections were incubated with an HRP conjugate secondary antibody (Neobioscience, Beijing, China) at 37°C for 10 minutes. Finally, Streptavidin-peroxidase (Neobioscience) was added and incubated at 37°C for 10 minutes. DAB was used for color development. After counterstaining with hematoxylin, hydrochloric acid differentiation, and dimethylbenzene transparency, sections were mounted with neutral gum. Positive control was set up. In the negative control, the primary antibody was replaced with PBS.

2.3. Evaluation of immunohistochemistry results

MTA1 protein was mainly expressed in the cell nucleus. Cells with yellow or brown staining were MTA1 positive cells. The degree of staining was evaluated based on the percentage of positive staining and the intensity of staining. Based on the percentage of positive staining, immunohistochemistry staining results were scored as follows: score 0 if the number of positive staining of glandular epithelial cells or stromal cells in the tissue was $< 5\%$. Score 1 when $5\% \leq$ positive staining $< 25\%$. Score 2 if $25\% \leq$ positive staining $< 50\%$. Score 3 when $50\% \leq$ positive staining $< 75\%$. Score 4 if positive staining cells $\geq 75\%$. Based on the staining intensity, immunohistochemistry staining results were scored as follows: Score 0 if negative staining. Score 1 when weak positive, light yellow. Score 2 if moderate positive, yellow. Score 3 if strong positive, brown. The final scores of staining were calculated by multiplying the scores obtained by the staining percentage and intensity, which ranged from 0 to 12 points. The final score 0 was defined as negative (–), 1 to 3 as weakly positive (+), 4 to 6 as positive (++), 7 to 9 as moderately positive (+++), and 10 to 12 as strongly positive (++++).

2.4. Reverse transcription-PCR (RT-PCR)

Total RNA was extracted by TRIzol (CST) method and reverse transcribed into cDNA according to reverse transcription kit (CST). The upstream primer for MTA1 was 5'-ATATCTTG CCGTGCTTCG-3', and the downstream primer was 5'-CCCGTTGTGCTGCTCGTA -3'. The primers for internal reference β-actin were F: 5'-GTGACGTTGACATCCGTAAA-GAC C-3' and R: 5'-GCTAGGAGCCAGGCAGTAATCT -3'. Two-step PCR amplification was used. The reaction conditions were set as follows: pre-denaturation at 95°C for 5 minutes, 95°C for 15 s, 60°C for 1 minute, 45 cycles. We use $2^{-\triangle\triangle ct}$ method to analyze the relative mRNA expression of each gene. The experiment was repeated 3 times.

2.5. Statistics

All data were analyzed by SPSS 17 (IBM, Armonk, NY, USA). The data were shown as mean ± SD. The Least Significant Difference (LSD)-t test was used for comparison among groups. The χ^2 test was used for analysis of the counting. Wilcoxon method was used for analysis of menstrual phase and r-AFS classification. Then we used single factor and multivariate Logistic regression analysis for the relationship between MTA1 expression and recurrence. $P < .05$ was considered as statistically significant.

Table 1

Clinical data of the 2 groups.

Groups	N	Age, y	BMI	Menstrual cycle	Abortion history	Dysmenorrhea history
Control group	100	31.10 ± 7.89	22.63 ± 3.81	29.45 ± 2.80	14%	51%
Endometriosis group	100	30.52 ± 8.38	21.97 ± 4.12	30.55 ± 3.32	19%	62%
t/χ^2	–	−1.682	1.317	−1.346	0.907	2.462
P	–	.096	.201	.194	.341	.117

BMI = body mass index.

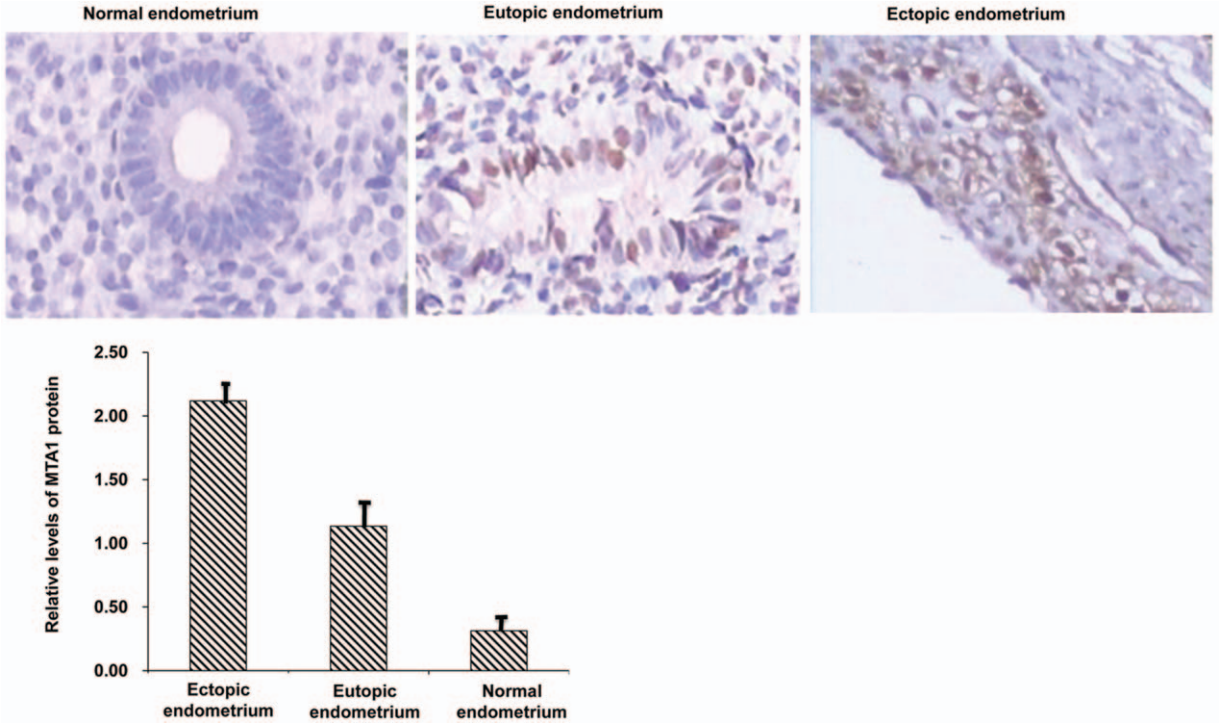

Figure 1. MTA1 expression in different endometrial tissues. MTA1 protein expression was detected with immunohistochemistry. Expression of MTA1 in normal endometrium, eutopic endometrium and ectopic endometrium was shown. Magnification, × 400. Relative MTA1 expression was shown in the lower panel.

3. Results

3.1. Expression of MTA1 in different endometrium

To determine the expression and location of MTA1 in endometrium, immunohistochemical staining was conducted. The results showed that the MTA1 level was the highest in ectopic endometrium and moderate in eutopic endometrium (Fig. 1). While MTA1 level was barely detectable in normal endometrium. The difference between the 3 groups was statistically significant ($P < .05$) (Fig. 1). The expression level of MTA1 mRNA was detected by RT-PCR. As shown in Table 2, the MTA1 mRNA level in ectopic endometrium, eutopic endometrium and normal endometrium were 2.119 ± 0.081, 1.434 ± 0.100 and 0.313 ± 0.008, respectively. The difference also showed statistical significance ($P < .05$). Thus, MTA1 protein and mRNA levels are increased in eutopic endometrium and ectopic endometrium.

3.2. MTA1 level in the menstrual cycle at different phases

During the menstrual cycle, the expression of MTA1 protein and mRNA in normal endometrium, eutopic endometrium and ectopic endometrium had no difference between proliferative phase and secretory phase ($P > .05$) (Table 3). The results showed that MTA1 had no relation with the proliferation and apoptosis of endometrium

Table 2

Comparison of MTA1 mRNA in different groups.

Groups	MTA1 mRNA level	*t*	*P*
Normal endometrium	0.313 ± 0.008	2.843	$< .05$
Eutopic endometrium	$1.434 \pm 0.100^{*}$	2.585	$< .05$
Ectopic endometrium	$2.119 \pm 0.081^{*,\dagger}$	3.184	$< .05$

Compared with normal endometrium.
* $P < .05$; compared with eutopic endometrium.
† $P < .05$.
mRNA = messenger RNA, MTA1 = metastasis-associated gene 1.

3.3. The relationship of MTA1 mRNA and MTA1 protein level with the r-AFS stage of endometriosis

As shown in Table 4, the MTA1 mRNA and MTA1 protein level in ectopic endometrium at stage III-IV were higher than those at stage I-II and the difference was statistically significant ($P < .05$). The results showed that MTA1 was directly proportional to the stage of endometriosis.

3.4. Single and multivariate logistic regression factors that affect the recurrence of ovarian endometriosis

The factors of age at operation, body mass index (BMI), rAFS stage, postoperative pregnancy, dysmenorrhea, and MTA1 expression were included into the single factor Logistic regression model for analysis. After that, the factors with $P < .05$ were included in the multivariate logistic regression model. The results showed that the r-AFS stage (odds ratio, OR = 2.43, 95% confidence interval, CI = 1.78–9.45) and the high expression of MTA1 (OR = 1.58, 95% CI = 1.16–3.04) were risk factors for the recurrence of endometriosis (Table 5). However, postoperative pregnancy (OR = 0.68, 95% CI = 0.45–0.91) was a protective factor for the recurrence of endometriosis.

4. Discussion

Endometriosis, like a malignant tumor, is invasive and capable of forming blood vessels at the distal end, thus leading to

Table 3

Endometrium MTA mRNA and protein level in different phases.

Groups	Phases	N	Number of cases with high MTA1 protein expression (%)	χ^2	P	MTA1 mRNA level	t	P
Normal endometrium	Proliferative phase	50	1	0.000*	>.05	0.305±0.006	0.633*	>.05
	Secretory phase	50	1			0.321±0.009		
Eutopic endometrium	Proliferative phase	45	19	1.375†	>.05	1.490±0.103	–0.782†	>.05
	Secretory phase	55	17			1.378±0.096		
Ectopic endometrium	Proliferative phase	45	37	0.512‡	>.05	2.095±0.078	0.875‡	>.05
	Secretory phase	55	42			2.142±0.083		

* Comparison between proliferative phase and secretory phase in normal endometrium group.
† Comparison between proliferative phase and secretory phase in eutopic endometrium group.
‡ Comparison between proliferative phase and secretory phase in ectopic endometrium group.
mRNA = messenger RNA, MTA1 = metastasis-associated gene 1.

Table 4

Relationship between MTA1 expression and r-AFS staging in ectopic endometrium.

Stages	N	MTA1 protein level					U	P	MTA1 mRNA level	t	P
		–	+	++	+++	++++					
I–II	38	0	18	18	2	0			1.992±0.079		
III–IV	62	0	3	11	19	29	227.00	<.05	2.246±0.083	2.113	<.05

MTA1 = metastasis-associated gene 1, r-AFS = American Society of Reproductive Endometriosis Staging.

endometriosis or even metastasis to the lungs and nasal cavity.[15,16] MTA1 is highly expressed in many malignant tumors, especially epithelial-derived endometrial cancer,[14] breast cancer,[17] gastrointestinal cancer,[18] prostate cancer,[19] salivary gland carcinoma,[20] and other malignancies.

Yuan et al[21] reported that silencing MTA1 expression could inhibit the migration and invasion of the gastric cancer cell line SGC7901, but could not affect cell proliferation. The same conclusion was obtained in ovarian cancer cell line A2780.[22] Moreover, the high expression of MTA1 is positively correlated to ovarian cancer FIGO clinical stage, lymph node metastasis and ascites.[23] The 5-year survival rate of patients with positive MTA1 expression in ovarian epithelial tumors is significantly lower than that in negative expression.[23] In early non-small cell lung cancer, MTA1 also plays an important role.[24–27] Studies have shown that MTA1 expression is significantly positively correlated to tumor size, infiltration, lymph node metastasis and micro-vessel density.[24,27] At the same time, survival analysis showed that the 5-year disease-free survival rate of MTA1-overexpressing patients was significantly lower than that of MTA1-negative or overexpression patients.[28] Multivariate analysis by COX regression showed that the high expression of MTA1 protein was negatively correlated with 5-year disease-free survival rate.[28] Thus, MTA1 is considered as a potential predictor of high recurrence risk and also a potential target for anti-angiogenic therapy.

In this study, immunohistochemistry (IHC) staining and RT-PCR showed that MTA1 was highly expressed in ectopic endometrium, which was significantly higher than that in both eutopic endometrium and normal endometrium, indicating that the high expression of MTA1 is involved in the malignant behavior of the ectopic endometrium. Study has shown that in colorectal cancer,[29] the adjacent lymphatic vessel density increased with MTA1 overexpression, suggesting that MTA1 high expression is closely related with the lymph angiogenesis and lymph node metastasis. However, whether endometriosis can metastasize through lymph node and whether MTA1 participates in this process remains to be further studied. There was no significant difference in the levels of MTA1 in the proliferative phase and the secretory phase in each group, indicating that MTA1 does not participate in the proliferation of endometrial cells, which is consistent with report by Yuan et al.[21]

According to the clinical data, we divided 100 patients with ovarian endometriosis into r-AFS stage of grade I, grade II, grade

Table 5

Univariate and multivariate Logistic regression models.

Factors	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age at operation	0.89	0.35–2.16	.432			
Body mass index	1.89	0.56–3.62	.276			
Postoperative pregnancy	0.63	0.42–0.89	.041*	0.68	0.45–0.91	.038*
Dysmenorrhea	2.13	0.72-3.66	.188			
MTA1 level	1.46	1.12-4.25	.014*	1.58	1.16-3.04	.018*
r-AFS	2.06	1.35–10.66	.003*	2.43	1.78–9.45	.002*

* $P<.05$.
CI=confidence interval, MTA1 = metastasis-associated gene 1, OR= odds ratio, r-AFS = American Society of Reproductive Endometriosis Staging.

III, and grade IV, among which 38 cases were in mild phase of grade I-II and 62 were in severe phase of grade III-IV. We found that the expression of MTA1 was closely related to the r-AFS stage of endometriosis. Thus, we included the patient's age, BMI, r-AFS grading, postoperative pregnancy, dysmenorrhea, and other factors into the single factor Logistic regression model. Through analysis, we found that the patient's age at surgery, BMI and dysmenorrhea was not related with the recurrence of endometriosis. This is different from the results of Maul et al,[30] which indicates that the lower the operative age, the greater the risk of recurrence. However, some studies have found that the younger patients with endometriosis, the lower the recurrence rate.[31,32] This difference may be resulted from the different distribution of the ages and other factors. Therefore, studies with larger sample sizes are warranted. After that, we included the factors with a $P < .05$ into the multivariate logistic regression model and found that high expression of MTA1 and rAFS grade were high risk factors for postoperative recurrence for ovarian endometriosis whereas pregnancy was a protective factor for the recurrence. However, Moini et al[33] found no correlation between rAFS grade and postoperative recurrence. In our opinion, this may be caused by the difference in grading standards among cases. So far, whether high expression of MTA1 is a further risk factor for postoperative recurrence of ovarian endometriosis is less studied, though it is considered as a predictor of high risk of recurrence in a variety of malignancies.

In summary, MTA1 protein is involved in the development of endometriosis. MTA1 protein may be of important significance for the clinical monitoring of ectopic endometrial invasion, metastasis and growth. Thus, MTA1 may be used as a molecular maker to predict the progression of EMs.

Author contributions

JZ conducted the experiments analyzed the data and wrote the article. HW performed the immunohistochemistry. QM extracted RNA and performed RT-PCR. JC and contributed to the collection of data. SH designed the research and revised the article.

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