

The expression of tissue inhibitors of metalloproteinase-2 (TIMP-2) in epithelial serous ovarian tumors

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Objective : Tissue inhibitors of metalloproteinases (TIMPs) play a key role in maintaining homeostasis of the extracellular matrix (ECM) by controlling matrix metalloproteinases (MMPs). In addition to their role in regulating MMPs, TIMPs have also been shown to have pluripotential effects on cell growth, apoptosis and differentiation. The aim of this study was to examine TIMP-2 level in serous ovarian tumor tissues and to understand further the role of TIMP-2 protein in ovarian tumorigenesis.

Methods : Expression of TIMP-2 was assessed by immunohistochemistry in a total of 57 ovarian specimens including five normal ovaries, 12 benign serous cystadenomas, 20 serous borderline tumors and 20 serous carcinomas.

Results : The present study found that TIMP-2 immunostaining was significantly more frequent in serous carcinomas, mainly in tumor epithelium, compared with cells of the other tissues studied.

Conclusion : TIMP-2 in serous ovarian carcinoma may function to favor tumor growth in serous ovarian tumorigenesis. Additional research is now needed to elucidate further the role of TIMP-2 in the biological behavior of ovarian serous tumors.

Key Words : TIMP-2, Ovarian Neoplasms, Serous Tumor, Immunohistochemistry

INTRODUCTION

Degradation of extracellular matrix (ECM) is an essential step in the process of angiogenesis, cellular invasion and tumor metastasis. The matrix metalloproteinases (MMPs), a family of structurally related zinc-dependent endoproteinases, are widely accepted to play a key role in these processes.¹ Under normal conditions, MMPs are tightly regulated at the level of gene transcription, activation of inactive zymogens, and inhibition by tissue inhibitors of metalloproteinases (TIMPs).²

The major role of TIMPs is known to control MMPs activity by forming high-affinity complexes with the active forms of MMPs as well as controlling the activation process

of MMPs.³ Therefore, the MMPs/TIMPs balance is critical for the maintenance of the ECM. These properties identified with the MMPs/TIMPs have led to the development of synthetic MMP inhibitors for potential cancer drug therapy; however, the results of these potential treatments have so far been disappointing.⁴ In addition to controlling MMPs, the TIMPs have been shown to have pluripotential effects on cell growth, apoptosis and differentiation.^{5,6} The effects of TIMPs on tumorigenesis are multifunctional and paradoxical. In contrast to their anti-MMP, anti-tumor effect, TIMP may also function in favor of tumor growth either in a MMP-independent or a MMP-dependent manner (Fig. 1).⁶

TIMPs form a family of at least four members, TIMP-1, -2, -3 and -4. They are two-domain molecules, having an amino-terminal domain of about 125 amino acids and a smaller carboxyl-terminal domain of about 65 residues.⁷ TIMP-1, -2 and -4 are secreted in soluble form, whereas TIMP-3 is insoluble and is bound to ECM proteins.⁸ Despite their many basic similarities, they exhibit distinctive expres-

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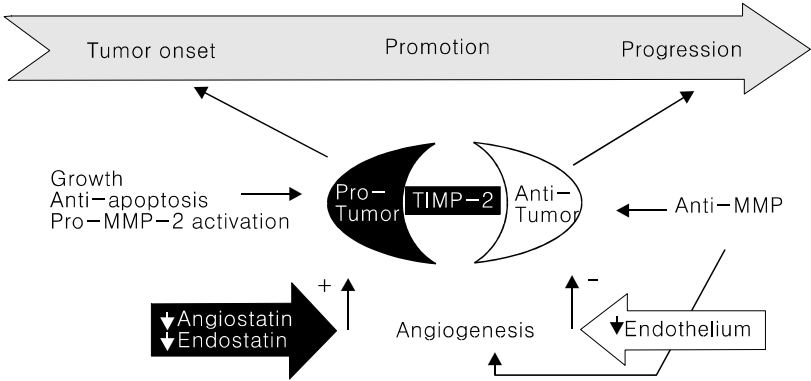


Fig. 1. Schematic illustration of the functions of TIMP-2 in tumorigenesis. While the anti-MMP activity of TIMP-2 is important in inhibiting tumor growth and particularly tumor malignant progression. TIMP-2 also have a growth stimulatory, anti-apoptotic effect, and participate in the pro-MMP-2 activation, which favor the tumor growth.⁶

sion patterns and phenotypic effects.⁵ In addition, their phenotypic effects may vary from cell to tissue. For example, TIMP-2 has erythroid potentiating activity,⁹ while it also acts to inhibit the growth of basic FGF-stimulated endothelial cells.¹⁰ In addition, it has been shown that TIMP-2 can promote apoptosis in an *in vivo* colorectal cancer model,¹¹ while it has been also shown to protect B16 melanoma cells from apoptosis.¹² There have been many studies on the phenotypic effects of TIMPs. However, there are only a limited number of reports on the molecular mechanisms, receptors and signaling pathways of TIMPs to date.¹³

Despite the well-known importance of TIMP-2 in the progression of carcinomas, few studies have examined TIMP-2 expression in ovarian cancer. Moreover, the findings of the few available reports on the expression patterns of TIMP-2 in ovarian cancer are not consistent.¹⁴⁻¹⁹ TIMP-2 expression in ovarian cancers seems to be variable and depends on the cell types studied and the detection methods employed.

The goals of this study were (1) to evaluate TIMP-2 levels in serous ovarian tumor tissues, and (2) to correlate the intensity of TIMP-2 staining in patients with serous ovarian carcinoma with pathologic parameters. To accomplish these goals, we analyzed TIMP-2 expression level using immunohistochemistry (IHC) and reviewed medical records of patients with serous ovarian carcinoma.

Table 1. Clinicopathological characteristics of 20 patients with serous carcinoma

Median age at diagnosis (years) (range)	56.5 (43-74)
FIGO stage	
IIc	1 (5.0%)
IIlb	2 (10.0%)
IIlc	15 (75.0%)
IV	2 (10.0%)
Histologic grade	
I/II	0 (0%)
II/III	4 (20.0%)
III/III	16 (80.0%)

FIGO: International Federation of Gynecology and Obstetrics

MATERIALS AND METHODS

1. Patients and tissues

Immunohistochemical staining was performed on surgical specimens obtained from patients with ovarian tumors and/or other gynecologic diseases. The operations were performed in the present hospital. A total of 57 ovarian specimens were collected including samples from five normal ovaries, 12 benign serous cystadenomas, 20 serous borderline tumors and 20 serous carcinomas. Study records were reviewed according to institutional review board guidelines. Characteristics from patients with serous carcinoma are shown in Table 1.

2. Immunohistochemistry

Formalin-fixed, paraffin-embedded 3 mm tissue sections

were prepared, deparaffinized in xylene and dehydrated through ethanol-water baths of increasing ethanol level. After washing with distilled water, antigen retrieval was achieved by autoclaving in the presence of 0.01 M citrate buffer for 10 min. After washing with Tris-buffered saline containing Tween 80 (TBS-T) endogenous peroxidase activity was blocked by 10 min of exposure to 3% (v/v) hydrogen peroxide (DAKO, Denmark). The slides were then incubated with a 1 : 25 dilution of primary anti-TIMP-2 mouse monoclonal antibody (Abcam, Cambridge, UK) at 4°C overnight and washed with TBS-T. Sections were developed with the ChemMate™ Envision™ detection kit (DAKO, Denmark) for 30 min at room temperature. After washing with TBS-T, the slides were incubated with the chromogen diaminobenzidine (DAKO, Denmark). The slides were counterstained with Meyer's hematoxylin.

The intensity of immunostaining was scored on a scale of 0 to 2+, where 0 denoted no staining; 1+ weak staining and 2+ intense staining. Both tumor epithelium and tumor stroma were examined. Two investigators (Choi YL and Kim TJ), both unaware of the origins of slide tissue samples, independently reviewed the slides and evaluated immunostaining intensities. The agreement between the two reviewers was very strong.

3. Statistical analysis

Statistical calculations were carried out using SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL). To analyze immunohistochemical results, the Kruskal-Wallis test was used to know significant difference between groups studied, and the Least Significant Difference test was applied for multiple comparisons among the four groups. A p value of <0.05 was considered to be statistically significant.

RESULTS

1. Immunohistochemical expression of TIMP-2 protein in serous ovarian tumors

Immunohistochemical expression of TIMP-2 was examined in 52 serous ovarian tumors (12 benign, 20 borderline,

Table 2. Results of immunohistochemical analysis for TIMP-2 in ovarian tissues

	TIMP-2 staining			Total
	0	1+	2+	
Epithelium				53*
Normal [†]	4 (100.0%)			4
Serous cystadenoma [‡]	7 (77.8%)	2 (22.2%)		9
Borderline serous tumor [§]	7 (35.0%)	11 (55.0%)	2 (10.0%)	20
Serous carcinoma	5 (25.0%)	5 (25.0%)	10 (50.0%)	20
Stroma				57
Normal	5 (100.0%)			5
Serous cystadenoma	11 (91.7%)	1 (8.3%)		12
Borderline serous tumor	20 (100.0%)			20
Serous carcinoma	15 (75.0%)	5 (25.0%)		20

*Four slides have no epithelial lining in the surface, [†]-^{||} (p=0.02), [‡]-^{||} (p=0.000), [§]-^{||} (p=0.025) by multiple comparison

20 malignant) and five normal ovaries. The results are summarized in Table 2. Epithelial ovarian tumor cells showed intracytoplasmic and membranous staining for TIMP-2 (Fig. 2). Stromal expression of TIMP-2 was also observed in some specimens, especially in the serous carcinomas (Fig. 2H). When the 4 groups (normal, benign, borderline and cancer) of specimens were compared with regard to the intensity of positive staining, the expression of TIMP-2 was significantly greater in serous carcinomas compared with the other groups (p=0.02, p<0.001, p=0.025, respectively) (Fig. 3).

2. Correlation between TIMP-2 staining and pathologic parameters in serous carcinomas

There was no correlation between the intensity of TIMP-2 immunostaining and international federation of gynecology and obstetrics (FIGO) stage or histologic grade in these tissues studied (p=0.788, p=0.441, respectively).

DISCUSSION

Our findings showed that TIMP-2 is up-regulated in serous

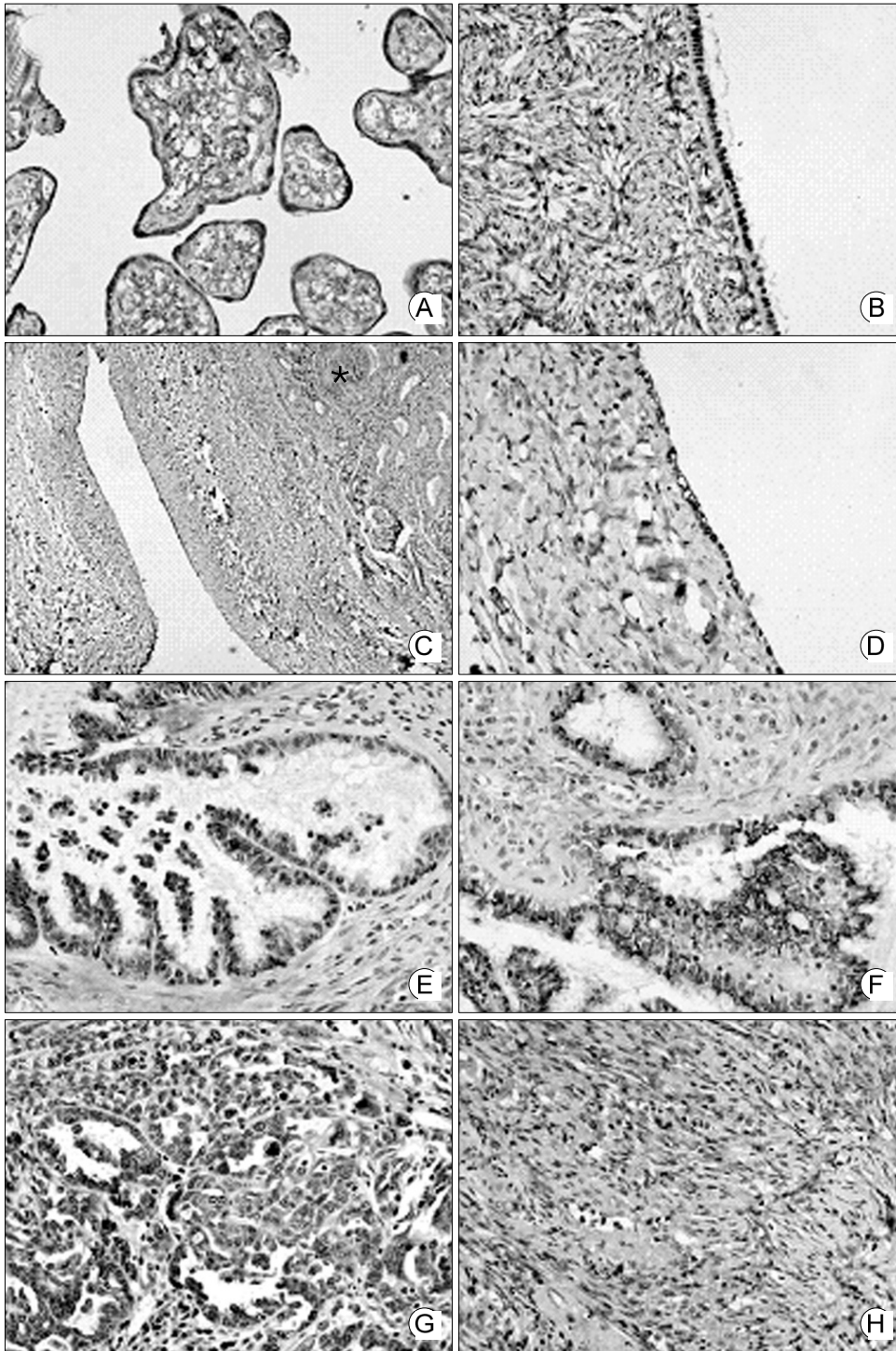


Fig. 2. Representative examples of TIMP-2 staining in serous ovarian tumors. (A) TIMP-2 was detected in cytotrophoblast cells and in endothelial cells (positive control, placenta, $\times 200$). (B) No staining was noted in normal ovarian epithelium or stroma ($\times 200$). (C) and (D), Weak staining of TIMP-2 in epithelial tumor cells of a serous cystadenoma. Smooth muscle cells of the vessel wall (*) also showed staining of TIMP-2; the intensity was graded as weak ($\times 40$, $\times 200$, respectively). (E) and (F) Weak staining of TIMP-2 in a borderline serous tumor (E, $\times 200$) and intense staining in another borderline serous tumor (F, $\times 200$). However, there was no staining in the stroma. (G) and (H), Serous carcinoma cells expressed intense staining of TIMP-2 (G, $\times 200$) and cancer stromal cells showed weak staining (H, $\times 200$).

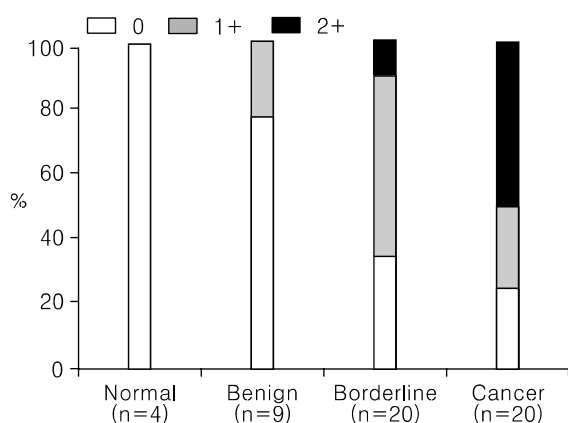


Fig. 3. Scoring of immunohistochemical TIMP-2 staining in normal ovaries, benign serous cystadenomas, borderline serous tumors and serous carcinomas. The expression of TIMP-2 was significantly more frequent in serous carcinomas compared with other groups ($p < 0.05$).

ovarian carcinoma when compared with normal ovaries, benign serous cystadenomas and serous borderline tumors. We could not find a significant correlation between TIMP-2 expression and FIGO stage or histologic grade in patients with serous carcinoma.

There have been numerous attempts to correlate MMPs and TIMPs expression with histologic types and grades of malignant tumors. This is especially true of MMP-2, MMP-9, TIMP-1 and TIMP-2. Reports of TIMP expression have been inconsistent and seem to depend on the tissues studied and the detection methods employed.^{6,14-17,20-29} While TIMPs exhibit anti-MMP activity, many investigators have reported MMP-independent mechanisms of TIMP action. TIMPs may also stimulate growth and antiapoptotic activities. In fact, TIMPs are very complex molecules with both protumor and antitumor actions. Diverse activities observed by many investigators may simply reflect the multifunctional properties of TIMPs. TIMPs may have a complex distribution because they are secreted proteins produced both by tumor cells and surrounding normal stromal cells.

Disease stage and histologic grade are well-known to have a prognostic value in ovarian carcinomas. However, the significant association between TIMP-2 expression and disease stage or histologic grade in ovarian carcinomas was not reported to date. Only a few studies have correlated

TIMP-2 expression with prognosis in ovarian carcinomas.^{18,19,29} Although Davidson, et al.^{18,19} suggested that TIMP-2 could be a valid marker for poor prognosis in advanced ovarian carcinoma, disease stage and histologic grade were not evaluated because of controlled study design. To examine further TIMP-2 effect on prognosis or pathologic parameters, we think MMPs levels should also be evaluated in the well designed study series.

A few studies have examined TIMPs or MMPs as factors contributing to ovarian tumorigenesis. Using immunohistochemistry, Sakata et al.¹⁴ suggested that the overexpression of MMP-2, MT1-MMP, TIMP-2 and MMP-9 and down-regulation of TIMP-1 may contribute to ovarian tumorigenesis. Davidson et al.^{18,19} showed that TIMP-2 expression correlated with poor survival using mRNA in situ hybridization and suggested that TIMP-2, MMP-2, MMP-9 and MT1-MMP are valid markers for prediction of poor survival in advanced ovarian carcinoma. Our results are consistent with the above studies. By contrast, Furuya et al.¹⁷ reported that both MMP-9 and TIMP-1 concentrations in mucinous cystic fluids are higher in carcinoma/borderline fluids than in adenoma fluids, but TIMP-2 is less prevalent in carcinoma/borderline fluids than in adenoma fluids. Kikkawa et al.¹⁶ showed that a high density band of TIMP-1 is observed in malignant tumor tissue when compared to normal ovary tissue, whereas there is no such change in the density of the TIMP-2 band as viewed by reverse zymography. Okamoto et al.¹⁵ demonstrated by ELISA that compared with those in the normal ovary, the TIMP-1 levels increase and TIMP-2 levels decrease in ovarian carcinomas, except for clear cell carcinomas, where TIMP-2 levels significantly increase. These observed differences of TIMP-2 expression may be due to different degrees of expression in different cell types, and the performance, by TIMP-2, of diverse functions during tumorigenesis. Furuya et al. studied mucinous ovarian tumors; Kikkawa et al. evaluated only three advanced serous carcinomas among 16 samples studied. Although Okamoto et al. examined 24 serous carcinomas among 66 malignant cases (30 stage I, four stage II, 23 stage III and nine stage IV) studied, these included many

early-stage cancers, and contralateral normal ovaries were often used as controls. In addition, Okamoto et al. employed ELISA, which may introduce a dilution effect on the expression of TIMP-2. TIMP-2 is known as a localized protein in both epithelial tumor cells and stromal cells adjacent to tumor epithelium. Because of this localization, a dilution effect from an unexpressed site may affect the decreased level of TIMP-2. In our work, we focused on serous ovarian tumors, which are the most common type of surface epithelial ovarian tumors. We chose a specific tumor type for study so that tissue variability would not complicate analysis of TIMP-2 expression.

TIMP-2 upregulation in serous ovarian carcinomas may be related to increased expression of MMPs during ovarian tumorigenesis. Previous studies have reported high expression of MMP-2, -9 in serous ovarian carcinoma.^{25,30,31} This up-regulation of TIMP-2 may represent an acute host response to remodeling stimuli and may represent an attempt to inhibit local tissue degradation. Since TIMP-2 staining was localized mainly in tumor epithelium and not in the stroma, we suggest that host responses to increased TIMP-2 in serous ovarian tumorigenesis may be weak. Alternatively, increased TIMP-2 expression may favor serous ovarian tumorigenesis by stimulating cell growth, by functioning to inhibit apoptosis, and by pro-MMP-2 activation.⁶

In summary, we found the high level of expression of TIMP-2 in serous ovarian cancers using IHC. Additional studies are now needed to elucidate further the role of TIMP-2 in the biology of ovarian serous tumors.

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상피성 장액성 난소 종양에서 Tissue inhibitors of metalloproteinase-2 (TIMP-2)의 발현 양상

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목적 : Tissue inhibitors of metalloproteinases-2 (TIMP-2)는 matrix metalloproteinases (MMPs)를 조절함으로써 종양의 성장 및 진행을 저해하는 데 중요한 역할을 한다고 알려져 왔으며, 최근에는 MMPs 조절 기능 외에 세포의 성장, 사멸 및 분화 과정에서 다양한 역할을 한다고 보고되어 왔다. 난소 종양에서는 TIMP-2에 관한 연구가 많지 않으며, 그 결과 또한 이견이 있는 상태로 조직 형태에 따라 TIMP-2의 발현 양상이 다를 수 있음이 보고되어 왔다. 따라서 본 연구는 난소 종양 중 상피성 장액성 종양 조직에 국한하여 TIMP-2의 발현 양상을 조사하고, 그 기능을 고찰하고자 하였다.

연구 방법 : 정상 난소 5예, 양성 장액성 낭선종 12예, 경계성 장액성 낭선종 20예, 장액성 선암 20예를 포함한 총 57예의 난소 조직을 대상으로, 면역조직화학염색법으로 TIMP-2의 발현 양상을 조사하였고, 이 결과와 병리 양상과의 상관관계를 알아보았다.

결과 : 장액성 선암에서의 TIMP-2의 발현 정도가 정상 난소, 양성 장액성 낭선종 및 경계성 장액성 낭선종과 비교하여 의미있게 높게 나타났으며($p=0.02$, $p<0.001$, $p=0.025$, 각각), 장액성 선암 환자들의 병기 및 조직 분화도와 TIMP-2의 발현 정도는 상관관계를 보이지 않았다($p=0.788$, $p=0.441$, 각각).

결론 : TIMP-2는 장액성 선암 조직에서 정상 난소, 양성 장액성 낭선종 및 경계성 장액성 낭선종과 비교하여 높게 발현되었으며, 이러한 결과는 TIMP-2가 장액성 선암 세포에서는 종양의 성장을 돕는 방향으로 작용할 가능성을 시사하며, 이에 대해서는 향후 새로운 연구가 필요하리라 사료된다.

중심단어 : TIMP-2, 난소 종양, 장액성 종양, 면역조직화학염색