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Alterations in Mucin Expression in Ovarian Mucinous Tumors: Immunohistochemical Analysis of MUC2, MUC5AC, MUC6, and CD10 Expression

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The aim of this study was to evaluate the immunohistochemical expression of MUC2, MUC5AC, MUC6, and CD10 in ovarian mucinous adenoma (MA), mucinous borderline tumor (MB), and mucinous adenocarcinoma (MC), and to analyze the relationship between prognosis and these expressions. The expression of MUC2, MUC5AC, MUC6, and CD10 was evaluated by immunohistochemical analysis in 29 cases of MA, 29 cases of MB, and 26 cases of MC and scored based on the percentage of positive cells. Moreover, the ovarian mucinous tumors were classified into 4 phenotypes based on the staining patterns: intestinal, gastrointestinal, gastric, and unclassified patterns. The gastrointestinal pattern and the expression of MUC2 and CD10 increased from MA to MC. Conversely, the gastric pattern and MUC5AC expression decreased from MA to MC. Low MUC2 expression in MC was correlated with a better long-term survival rate. MUC2 expression in MC may be a useful predictor of the clinical outcome. The expression patterns of MUC2, MUC5AC, MUC6, and CD10 indicated that intestinal metaplasia may arise from the gastric-like epithelium in MA and that a close association exists between carcinogenesis and intestinal metaplasia in major ovarian mucinous tumors.

Key words: CD10, MUC2, MUC5AC, MUC6, ovarian mucinous tumor

I. Introduction

Ovarian mucinous tumors are composed of mucin-containing tumor cells and are classified into 3 types: mucinous adenoma (MA), mucinous borderline tumor (MB), and mucinous adenocarcinoma (MC) [16]. According to the current classification of the World Health Organization (WHO), MB is further classified into 2 types: the intestinal type (MBI) and endocervical-like (MBE) [16]. The former is mainly composed of intestinal-like epithelium that usually contains goblet cells, whereas the latter is mainly composed of tumor cells resembling endocervical columnar epithelium.

Mucins are high-molecular-weight glycoproteins containing oligosaccharides that are attached to an apomucin protein backbone via O-glycosidic linkages, and are synthesized in the glandular epithelium [1, 12, 17]. Mucins are classified into cell surface-associated mucin and gel-forming mucin [12, 20, 30]. MUC2, MUC5AC, and MUC6 represent gel-forming mucin, and are expressed in several secretory epithelia. CD10 was initially identified as the common acute leukemia antigen (CALLA) [15] and is widely expressed in epithelial and non-epithelial tissues.

Many studies have evaluated the combined expression patterns of MUC2, MUC5AC, MUC6, CD10, human gastric

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mucin, and M-GGMC-1 in the non-neoplastic or neoplastic epithelium of the stomach, gallbladder, intrahepatic biliary system, and Barrett's esophagus [5, 18, 19, 22, 23, 29, 32–34, 38, 40–42]. The gastric epithelium is usually positive for MUC5AC (gastric foveolar epithelium) and MUC6 (gastric pyloric gland) but negative for MUC2 [27, 39]. On the other hand, the goblet cells of the intestinal epithelium are generally positive for MUC2 but negative for MUC5AC and MUC6 [1, 2, 39]. The brush border of the small intestinal epithelium is positive for CD10 [37]. The expression pattern of MUC2, MUC5AC, MUC6, and CD10 in the endocervical glandular epithelium is similar to that in the gastric epithelium [3, 4, 13, 21, 28, 43].

Some studies in the literature have reported the expression of mucins in ovarian tumors [1, 8, 10, 11, 14, 20, 35]. However, determination of the phenotype based on the expression patterns of MUC2, MUC5AC, MUC6, and CD10 in ovarian mucinous tumors has not been well documented. Therefore, we evaluated the phenotype based on the immunohistochemical expression patterns of MUC2, MUC5AC, MUC6, and CD10 in ovarian mucinous tumors to determine whether a relationship exists between the expressions of MUC2, MUC5AC, MUC6, and CD10 and the prognosis of MC.

II. Materials and Methods

Tumor specimens

In this study, ovarian mucinous tumors surgically resected at the Tokai University Hospital between 1991 and 2006 were used. All tumors were classified according to the WHO classification [16]. The number and histological type of ovarian tumors were as follows: 29, MA; 29, MB; and 26, MC. There were 18 cases of MBI and 11 cases of MBE. The mean age of the MA patients was 39.1±2.8 years (range, 16–69 years) and that of MC patients was 47.8±3.0 years (range, 18–82 years). The mean age of the MB patients was 39.2±2.4 years (range, 18–72 years): MBI, 42.2±3.0 years (range, 24–72 years) and MBE, 34.4±3.8 years (range, 18–65 years). Ovarian cancer was classified into various stages according to the International Federation of Gynecology and Obstetrics (FIGO) classification [36]. The number of cases of each stage was as follows: stage I, 16 cases; stage II, 0 cases; stage III, 6 cases; and stage IV, 4 cases.

Immunohistochemical analysis

One representative section was selected for immunohistochemical staining based on the histological findings of the ovarian mucinous tumors. Each tissue was formalin-fixed, paraffin-embedded, and cut into 4-μm-thick sections. The sections were deparaffinized in xylene and rehydrated through a graded ethanol series to distilled water. The monoclonal antibodies used were MUC2 (clone Ccp58, dilution 1:100; Novocastra, Newcastle-upon-Tyne, UK), MUC5AC (clone CLH2, dilution 1:100; Novocastra), MUC6 (clone CLH5, dilution 1:100; Novocastra), and CD10 (clone 56C6, dilution 1:50; Novocastra). For antigen retrieval, each slide was boiled in citrate buffer (MUC2, MUC5AC, and MUC6, pH 6.0; CD10, pH 7.0) in a pressure cooker for 10 min. An automated immunostainer (Dako autostainer; Dako Japan Co. Ltd., Tokyo, Japan) was utilized for immunohistochemical staining. The antibodies were detected using the EnVision system (Dako Japan Co. Ltd.) with 3,3'-diaminobenzidine as the chromogen. Appropriate positive and negative tissue control samples were used.

Evaluation of immunohistochemical staining

Each staining was evaluated based on the proportion of positive cells as follows: 0, (negative); 1+, (less than 5%); 2+, (6–25%); 3+, (26–50%); 4+, (51–75%); and 5+, (76–100%). In addition, ovarian mucinous tumors were classified into the following 4 phenotypes based on the staining patterns of MUC2, MUC5AC, MUC6, and CD10: intestinal pattern (MUC2 and/or CD10: score 1+ to 5+ and MUC5AC and MUC6: score 0), gastrointestinal pattern (MUC2 and/or CD10: score 1+ to 5+ and MUC5AC and/or MUC6: score 1+ to 5+), gastric pattern (MUC2 and CD10: score 0 and MUC5AC and/or MUC6: score 1+ to 5+), and unclassified pattern (MUC2 and CD10: score 0 and MUC5AC and MUC6: score 0) (Fig. 1).

Statistical analysis

The data were analysed using the Tukey-Kramer test, paired *t* test, and Kruskal Wallis test. Survival distributions were estimated by Kaplan-Meier analysis. The log-rank test was performed to compare the survival times in MC according to the expression scores of MUC2, MUC5AC, MUC6, and CD10 and the 4 phenotypic patterns. $P<0.05$ was interpreted as significant. Statistical calculations were performed using SPSS 15.0J (SPSS Japan, Tokyo, Japan).

	MUC2 and/or CD10 Positive (score 1+ to 5+)	MUC2 and CD10 Negative (score 0)
MUC5AC and MUC6: Negative (score 0)	Intestinal pattern	Unclassified pattern
MUC5AC and/or MUC6: Positive (score 1+ to 5+)	Gastrointestinal pattern	Gastric pattern

Fig. 1. Four phenotypes based on the expression of MUC2, MUC5AC, MUC6, and CD10.

III. Results

Expression of MUCs and CD10 in ovarian mucinous tumors (Table 1 and Fig. 2)

MUC2

The proportion of MUC2-positive cells increased from MA and MB to MC. MC exhibited a higher proportion of MUC2-positive cells than MA (P=0.04); however, there was no significant difference in the proportion of MUC2-positive cells between MA and MB or between MB and MC. Goblet cells were mainly MUC2 positive; however, the proportion of MUC2-positive goblet cells was lower than that of the hematoxylin and eosin (H&E)-stained goblet cells.

MUC5AC

All cases of MA and MB were positive for MUC5AC, but MUC5AC expression in MC was significantly lower than that in MA and MB (P<0.001). MUC5AC was expressed in the cytoplasm of endocervical-like tumor cells. Furthermore, MUC5AC was also expressed in the cytoplasm of both MUC2-positive and MUC2-negative goblet cells. Mucinous tumors exhibiting a diffuse positive reaction for MUC2 were simultaneously positive for MUC5AC.

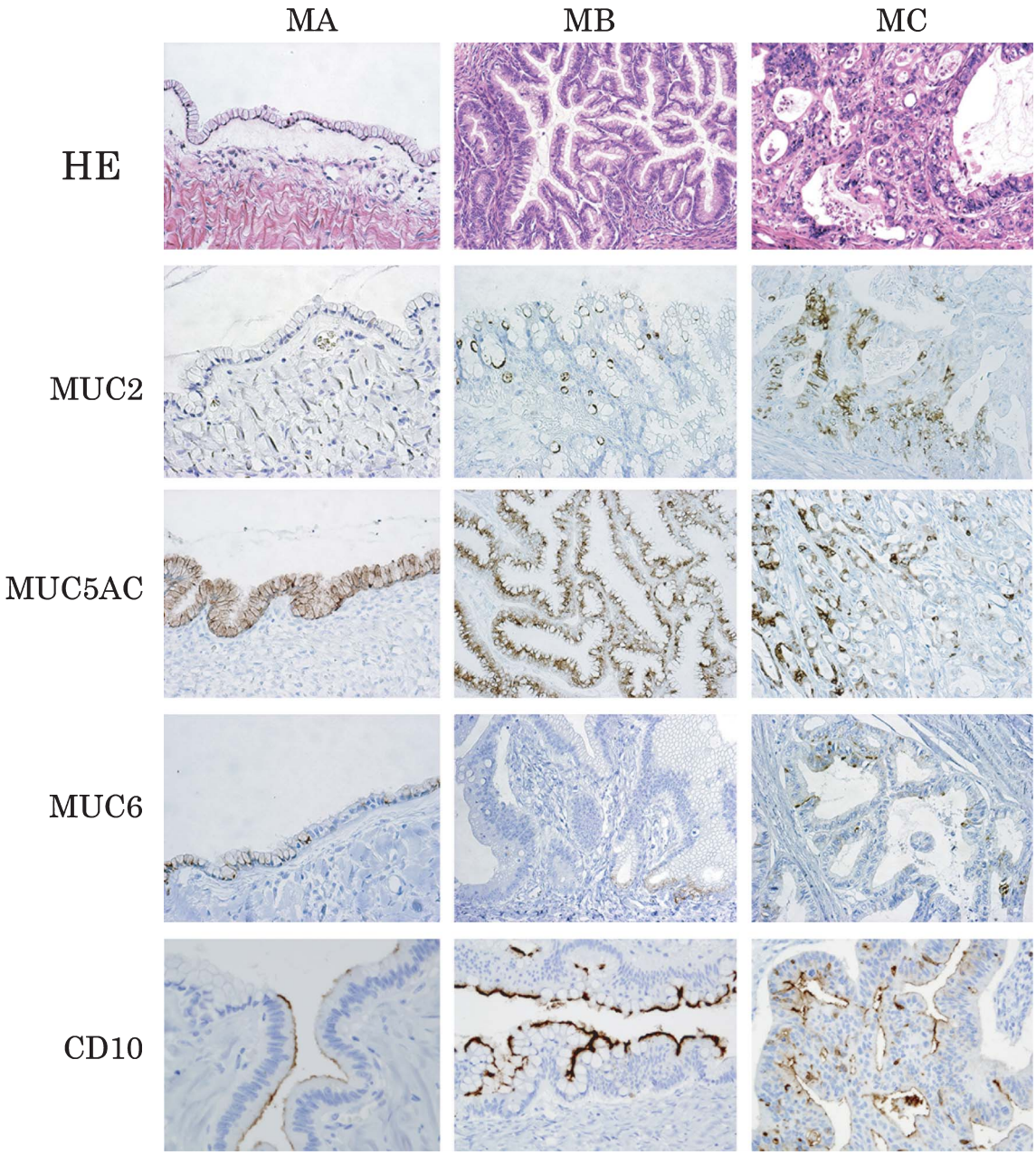

Fig. 2. Expression of MUC2, MUC5AC, MUC6, and CD10 in mucinous adenoma (MA), mucinous borderline tumor (MB), and mucinous adenocarcinoma (MC).

Table 1. *Comparison of MUC2, MUC5AC, MUC6, and CD10 expressions in mucinous adenoma (MA), mucinous borderline tumor (MB) and mucinous adenocarcinoma (MC)*

Antigen	MA (n=29)	MB (n=29)	MC (n=26)	Pairwise P-value			Overall P-value
		(mean score±SE)		MA vs. MB	MA vs. MC	MB vs. MC	
MUC2	0.4±0.2	0.9±0.2	1.2±0.3	0.231	0.04	0.66	0.046
MUC5AC	4.6±0.2	4.5±0.2	2.4±0.4	0.913	<0.001	<0.001	<0.001
MUC6	0.8±0.2	0.3±0.1	0.7±0.2	0.104	0.993	0.148	0.077
CD10	0.1±0.1	0.2±0.1	0.8±0.3	0.792	0.008	0.46	0.008

SE, standard error.

MUC6

MUC6 was expressed in the cytoplasm of endocervical-like tumor cells. The MUC6 score was very low in each histological type. There was no significant difference in the proportion of MUC6-positive cells among MA, MB, and MC.

CD10

The proportion of CD10-positive cells increased from MA and MB to MC (P=0.008). CD10 was mainly expressed in the apical membrane of the goblet cells or in tumor cells near the goblet cells. CD10 was expressed in both MUC2-positive and MUC2-negative tumor cells.

Expression of MUCs and CD10 in MB (Table 2)

MUC2 was expressed more strongly in MBI than in MBE (P<0.001). The expression of CD10 was higher in MBI than that in MBE; however, there was no significant difference in the expression of MUC5AC, MUC6, and CD10 between MBE and MBI. MUC5AC was diffusely expressed in both MBE and MBI.

Phenotypes based on the expression patterns of MUC2, MUC5AC, MUC6, and CD10 (Tables 3 and 4)

The gastrointestinal pattern increased from MA and MB to MC (P=0.002). On the other hand, the gastric pattern decreased from MA and MB to MC (P<0.001). The intestinal pattern was not observed in any histological type. The unclassified pattern was identified only in MC (3 cases, 11.5%) (P=0.032). Of the MB cases, 90.9% of the MBE cases demonstrated the gastric pattern and 83.3% of the MBI cases, the gastrointestinal pattern. No case of MBE or MBI exhibited the intestinal pattern or unclassified pattern.

Table 2. *Comparison of MUC2, MUC5AC, MUC6, and CD10 expression in mucinous borderline tumor of endocervical-like (MBE) and mucinous borderline tumor of the intestinal type (MBI)*

Antigen	MBE (n=11)	MBI (n=18)	P-value
	(mean score±SE)		
MUC2	0	1.5±0.3	<0.001
MUC5AC	4.2±0.4	4.6±0.2	0.262
MUC6	0.3±0.2	0.3±0.1	0.983
CD10	0.1±0.1	0.3±0.1	0.158

SE, standard error.

Correlation with patient survival

In MC, the low score, 0 to 2+, for MUC2 (n=22) was associated with a better long-term survival rate (P=0.025) (Fig. 3). In MC, no significant difference was observed in the survival rates among the expressions of MUC5AC, MUC6, and CD10 or among the intestinal, gastrointestinal, unclassified, and gastric patterns. No relationship was observed between the FIGO stage and the expression of MUCs and CD10 or the 4 phenotypic patterns.

IV. Discussion

The present study demonstrated that the gastrointestinal pattern increased but the gastric pattern decreased from MA to MC. The intestinal pattern was not observed in the mucinous tumors. The unclassified pattern was identified only in MC. In the MB cases, MBI and MBE were comparatively correlated with the gastrointestinal and gastric patterns, respectively.

The expression of the intestinal markers MUC2 and CD10 increased from MA and MB to MC. Previous studies in the literature also present similar data demonstrating that MUC2 expression increased concomitantly with the transition from MA to MC [1, 10, 11, 35]. Although Dong *et al.* [10] reported that no relationship existed between MUC2 expression and the prognostic data related to clear cell adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, serous adenocarcinoma, and mixed mesodermal tumor of the ovary, our results demonstrated that MC with a strong positive reaction for MUC2 was associated with a poor prognosis; however, no relationship was observed between CD10 expression and prognosis. In MC, the poor prognosis with a strong positive reaction for MUC2 might be related to the increase in MUC2 expression from MA to MC. Focusing on the relationship between MUC2 and p53, Ookawa *et al.* [24] suggested that MUC2 gene is activated by p53 in many cell types. Shimonishi *et al.* [31] reported that both MUC2 and p53 were expressed more frequently in intraductal papillary neoplasia of the liver than in nonneoplastic bile ducts. p53 may be a important role for MUC2 expression in the ovarian mucinous tumor.

The gastric marker MUC5AC demonstrated high

Table 3. *Mucinous adenoma (MA), mucinous borderline tumor (MB), and mucinous adenocarcinoma (MC) classified into intestinal, gastrointestinal, gastric, and unclassified patterns based on the staining patterns of MUC2, MUC5AC, MUC6, and CD10*

	MA (n=29)		MB (n=29)		MC (n=26)		P-value
	n	(%)	n	(%)	n	(%)	
Gastrointestinal pattern							
MUC2(+)/MUC5AC(+)/MUC6(−)/CD10(−)	2	(6.9)	8	(27.6)	4	(15.4)	
MUC2(+)/MUC5AC(+)/MUC6(+)/CD10(−)	1	(3.4)	3	(10.3)	3	(11.5)	
MUC2(+)/MUC5AC(+)/MUC6(+)/CD10(+)	3	(10.3)	1	(3.4)	5	(19.2)	
MUC2(+)/MUC5AC(+)/MUC6(−)/CD10(+)	0	(0)	4	(13.8)	3	(11.5)	
MUC2(−)/MUC5AC(+)/MUC6(+)/CD10(+)	0	(0)	0	(0)	1	(3.8)	
MUC2(−)/MUC5AC(+)/MUC6(−)/CD10(+)	0	(0)	1	(3.4)	0	(0)	
MUC2(−)/MUC5AC(−)/MUC6(+)/CD10(+)	0	(0)	0	(0)	1	(3.8)	
Total	6	(20.7)	17	(58.6)	17	(65.4)	0.002
Gastric pattern							
MUC2(−)/MUC5AC(+)/MUC6(−)/CD10(−)	12	(41.4)	10	(34.5)	5	(19.2)	
MUC2(−)/MUC5AC(+)/MUC6(+)/CD10(−)	11	(37.9)	2	(6.9)	1	(3.8)	
MUC2(−)/MUC5AC(−)/MUC6(+)/CD10(−)	0	(0)	0	(0)	0	(0)	
Total	23	(79.3)	12	(41.4)	6	(23.1)	<0.001
Unclassified pattern							
MUC2(−)/MUC5AC(−)/MUC6(−)/CD10(−)	0	(0)	0	(0)	3	(11.5)	0.032

Table 4. *Mucinous borderline tumor of endocervical-like (MBE) and mucinous borderline tumor of the intestinal type (MBI) were classified into intestinal, gastrointestinal, gastric, and unclassified patterns based on the staining patterns of MUC2, MUC5AC, MUC6, and CD10*

	MBE (n=11)		MBI (n=18)		P-value
	n	(%)	n	(%)	
Gastrointestinal pattern					
MUC2(+)/MUC5AC(+)/MUC6(−)/CD10(−)	0	(0)	8	(44.4)	
MUC2(+)/MUC5AC(+)/MUC6(+)/CD10(−)	0	(0)	3	(16.7)	
MUC2(+)/MUC5AC(+)/MUC6(+)/CD10(+)	0	(0)	1	(5.6)	
MUC2(+)/MUC5AC(+)/MUC6(−)/CD10(+)	0	(0)	3	(16.7)	
MUC2(−)/MUC5AC(+)/MUC6(+)/CD10(+)	0	(0)	0	(0)	
MUC2(−)/MUC5AC(+)/MUC6(−)/CD10(+)	1	(9.1)	0	(0)	
MUC2(−)/MUC5AC(−)/MUC6(+)/CD10(+)	0	(0)	0	(0)	
Total	1	(9.1)	15	(83.3)	<0.001
Gastric pattern					
MUC2(−)/MUC5AC(+)/MUC6(−)/CD10(−)	8	(72.7)	3	(16.7)	
MUC2(−)/MUC5AC(+)/MUC6(+)/CD10(−)	2	(18.2)	0	(0)	
MUC2(−)/MUC5AC(−)/MUC6(+)/CD10(−)	0	(0)	0	(0)	
Total	10	(90.9)	3	(16.7)	<0.001
Unclassified pattern					
MUC2(−)/MUC5AC(−)/MUC6(−)/CD10(−)	0	(0)	0	(0)	1.000

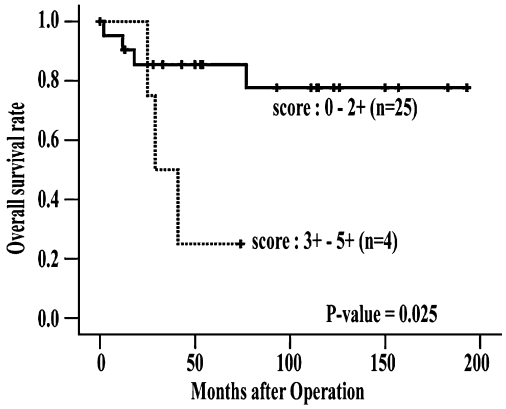

Fig. 3. Overall survival in MC cases according to the MUC2 score. A better long-term survival rate was noted for MC cases with a score of 0 to 2+.

scores for both MA and MB. On the other hand, the expression of MUC5AC decreased in MC. These results are similar to those of previous studies [1]. Based on our observations, it appears that no relationship exists between MUC5AC expression and prognosis in ovarian carcinomas. The other gastric marker MUC6 demonstrated very low scores in MA, MB, and MC in contrast to those demonstrated by MUC5AC. There was no significant increase or decrease in MUC6 expression from MA to MC, as observed for the other markers.

Interestingly, the expression patterns of MUC2 and MUC5AC in the ovarian mucinous tumors are similar to those in the endocervical glandular epithelium of the uterine cervix. Although the normal endocervical mucosa of the uterine cervix is usually positive for MUC5AC but negative for MUC2, MUC2 is expressed in endocervical adenocarcinoma; further, MUC5AC expression is lower in endocervical adenocarcinoma than in the normal endocervical mucosa [4, 28, 43]. It is possible that carcinogenesis in ovarian mucinous and endocervical adenocarcinomas is similar with regard to MUC expression.

Focusing on the immunohistochemical expression in the goblet cells of the ovarian mucinous tumor, most of these cells were MUC2 positive/MUC5AC positive or MUC2 negative/MUC5AC positive in contrast to the intestinal goblet cells that were MUC2 positive and MUC5AC negative [39]. These findings revealed that most of the goblet cells identified upon H&E staining of the ovarian mucinous tumors were immature for mucin expression.

The abovementioned results suggest that MUC5AC is the basic mucin present in ovarian mucinous tumors and that intestinal metaplasia is accentuated from MA to MC. The location of MUC2 and MUC5AC on the same chromosome (11p15.5) may be related to the observation of intestinal metaplasia in ovarian mucinous tumors [1, 9]. Ovarian carcinoma may develop *de novo* or arise from a pre-existing benign epithelium [6, 7, 25, 26]. The increase in the gastrointestinal pattern from MA to MC may suggest that carcinogenesis originated from the intestinal metaplasia in MA and MB. Otherwise, the presence of the gastric pattern in MB and MC may suggest the presence of other carcinogenesis pathways that are unrelated to intestinal metaplasia. In conclusion, the results of our study revealed 4 phenotypes based on the expression patterns of MUC2, MUC5AC, MUC6, and CD10 among MA, MB, and MC. The gastrointestinal pattern increased from MA to MC. In contrast, the gastric pattern decreased from MA and MB to MC. In addition, the low expression of MUC2 in MC was associated with a better prognosis. These results suggested that the difference in MUC2 expression among MC cases may be useful in predicting the clinical outcome. Furthermore, the results indicated that intestinal metaplasia may arise from the gastric-like epithelium in MA and that carcinogenesis is probably related to intestinal metaplasia. On the other hand, the presence of the gastric pattern suggests the possibility of carcinogenesis unrelated to intestinal metaplasia.

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VI. References

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