



Correlation of Expression of SATB2 and CK20 in Mucinous Ovarian Tumors with their Pathological Classification and Prognosis

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ABSTRACT

This study aims to evaluate the co-expression of specific AT sequence binding protein 2 (SATB2 Group) and Cytokeratin 20 (CK20 Group) in mucinous ovarian tumors and their correlation with tumor pathological classification and prognostic outcome. One hundred and sixty cases of ovarian mucinous tumors diagnosed from January 2018 and January 2020 were selected. They were divided into four groups: mucinous cystadenocarcinoma group (age 62.78 ± 7.92 , $n=53$), borderline mucinous cystadenocarcinoma group (age 63.82 ± 9.26 , $n=55$), mucinous cystadenocarcinoma group (age 62.81 ± 6.28 , $n=52$) Group and normal ovarian group (age 62.71 ± 7.97 , $n=160$). All cases were examined by two gynecological pathologists. The expression levels of SATB2 and CK20 in different groups were detected by immunohistochemical staining. SATB2 in mucinous ovarian tumors had a diagnostic sensitivity of 82%, a specificity of 78%, and an overall accuracy rate of 82%. CK20 in mucinous ovarian tumors had a diagnostic sensitivity of 94%, a specificity of 59%, and an overall accuracy rate of 85%. SATB2/CK20 in mucinous ovarian tumors has a diagnostic sensitivity of 65%, a specificity of 99%, and an overall accuracy rate of 89%. Compared with SATB2/CK20 single staining, SATB2/CK20 double staining had lower sensitivity, higher specificity and increased overall accuracy. The expression levels of SATB2 and CK20 were not related to the patient's age, menstrual status and tumor diameter ($P>0.05$), but was related to recurrence, pathological type, tissue differentiation, prognostic outcome, disease course and clinical stage ($P<0.05$). According to immunohistochemical examination, the co-expression of SATB2 and CK20 could improve the specificity of mucinous ovarian tumors. In addition, SATB2/CK20 co-expression is related to recurrence, pathological type, tissue differentiation, prognostic outcome, disease course and clinical stage.

Article Information

Received 02 February 2021

Revised 19 March 2021

Accepted 25 March 2021

Available online 07 October 2021
(early access)

Published 19 February 2022

Key words

Mucinous tumors of the ovary,
Specific AT sequence binding protein
2, Cytokeratin 20, Pathological typing,
Prognostic outcome.

INTRODUCTION

The morphology of mucinous tumors in various sites is similar to that of glandular epithelial cells and extracellular mucins which produce mucilage. Although most mucinous tumors originate from gastrointestinal tract, they may also originate from breast, lung, pancreas and gynecology. Mucous tumors often metastasize to ovary, peritoneal surface, liver or lung (Stewart *et al.*, 2020). Sometimes, the main origin of mucinous tumors found in peritoneum or pelvic cavity is difficult to identify. Pathologists face challenges in daily practice of ovarian mucinous tumors. When most well-differentiated tumors are observed, the possibility of metastatic tumors is often ignored (Zhu *et al.*, 2020). A study found that 70% of cases initially diagnosed as primary tumors can be reclassified as metastatic mucinous cancer with extraovarian diseases (Nazari and Dehghani, 2020). Besides macroscopic and

microscopic features, immunohistochemical staining can also be used for differential diagnosis. SATB2 and CK20 are the most commonly used markers (Meagher *et al.*, 2019). SATB2 is a human DNA binding protein with 733 amino acids. It is involved in transcription regulation and chromatin remodeling, and its expression is limited to glandular cells in the lower gastrointestinal tract (Halimi *et al.*, 2021). Recent studies have shown that SATB2 is a sensitive and highly specific marker of colorectal cancer, with different positive rates in 85% of all colorectal cancers, and the combination of SATB2 and CK20 can recognize 97% of colorectal cancers (Matsuo *et al.*, 2019). The studies also show that the incidence of ovarian cancer is 3.3%, and the incidence of ovarian cancer is 5.7%. Among lung adenocarcinoma, SATB2 is positive, while SATB 2.2 in all gastric cancer and pancreatic cancer were negative. Other studies have shown that the down-regulation of SATB2 expression is related to the metastasis and poor prognosis of colorectal cancer (Kurnit *et al.*, 2019). SATB2 is also a marker of osteoblast differentiation in benign and malignant mesenchymal tumors (Bhuyan *et al.*, 2019). Mucous tumors express low molecular weight cytokeratin,

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0030-9923/2022/0003-1171 \$ 9.00/0

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such as CK7, CK8, CK18 and CK20, among which CK20 has the highest diagnostic value (Alghamdi *et al.*, 2020). Generally, low gastrointestinal mucinous tumors express CK20 (Zhang *et al.*, 2019). CK20 is expressed in 47% to 83% of ovarian mucinous tumors. In view of the high sensitivity and specificity of SATB2 and CK20 in rectal cancer, and the challenge in distinguishing abdominal/pelvic mucinous tumors, we explored the expression of SATB2 and CK20 in mucinous ovarian tumors by using double staining and a nuclear stain SATB2 combined with cytoplasmic stain CK20 in this study. We also compared their sensitivity and specificity to determine whether any combination could provide improved diagnostic utility, and studied their correlation with tumor pathological classification and prognostic outcome.

MATERIALS AND METHODS

General data

The research team covered 160 cases of ovarian mucinous tumors diagnosed between January 2018 and January 2020. The research was divided into four groups: mucinous cystadenocarcinoma group (age 62.78±7.92, n=53), borderline mucinous cystadenocarcinoma group (age 63.82±9.26, n=55), mucinous cystadenocarcinoma group (age 62.81±6.28, n=52), and normal ovarian group (age 62.71±7.97, n=160).

Inclusion criteria: Patients diagnosed as ovarian mucinous tumors; aged 45 to 75 years old; immunohistochemical staining was performed in all patients.

Exclusion criteria: Cases with suspected metastasis (bilateral tumor, less than 13 cm, mucus on the surface, lymphatic infiltration) were found according to pathology, but no proper clinical research or follow-up was conducted; patients who have not signed informed consent.

Medical ethics

This study had obtained the informed consent of patients, was examined and approved by the institutional review committee of the National Cancer Institute, and has been carried out in accordance with the Helsinki Declaration.

Clinical information collection

Clinical information, such as age and previous tumor history, was collected. Tumor data such as size, laterality, presence of extraovarian disease and occurrence of capsule disease were also reviewed. Only confirmed primary, previous, synchronous or metastatic tumors after ovarian surgery were included.

Immunohistochemical staining

All cases were examined by two gynecologic pathologists, and slides with a large amount of epithelial components were selected. Because of the mucus in tumor, the whole section of paraffin block was used to determine the percentage of protein expression. The following antibodies were used in this study: mouse IgG monoclonal antibody SATB2 (SATBA4B10, 1:25, SC-81376; Santa Cruz, CA) and CK20 (1:50, CM062C; Dako). For CK20, the slides with 3µm sections were degreased at 60°C overnight and placed in an automatic staining instrument (Benchmark Ultra; Ventana Medical Systems, Tucson, Arizona). For CK20, the slides with 3µm sections were degreased at 60°C overnight and placed in an automatic staining instrument (Benchmark Ultra; Ventana Medical Systems, Tucson, Arizona). For SATB2, the slides with 3µm slices were separated overnight at 60°C and placed in xylene for 5 min. The slides were rehydrated in reduced alcohol (96%, 80.70% and 60%) and washed in water. Citrate buffer (pH 6.0) was used in a pressure cooker in a microwave oven to achieve epitope repair. The activity of endogenous peroxidase was blocked by 0.3% hydrogen peroxide. Glass slides were washed with phosphate buffered saline (PBS). Anti-SATB2 in a 1:25 dilution was used to incubate the slides with the primary antibody at 37°C for 45 min, and the slides were washed with PBS. Mach 4 mouse probe (Biocare) was added at 37°C for 15 min, and the slides were washed with PBS for 5 min. Then, Mach 4 HRP polymer (Biocare) was added at 37°C for 15 min. Glass slides were washed with PBS for 5 min and exposed with 3,3'-diaminobenzidine (Biocare). After that, the slide were washed in water, counterstained with hematoxylin, dehydrated and fixed. Normal colon mucosa was used as positive control. When protein expression existed in less than 20% of tumor cells, whether protein expression was a lesion could be evaluated at will. The intensity of immunostaining was observed, but it was not used for scoring. We made descriptive statistics on demographic variables, and reported the centralized trend measure. We used continuous variables of student's t test and ordinal variables of χ^2 or Fisher's exact test to conduct univariate analysis of the mean value.

Semi-quantitative score of reaction mode

The tumor was scored by semi-quantitative method according to the following scheme: 0 (no signal in any tumor cell); 1+ (positive signal of any intensity in less than 25% of the sampled tumor area); 2+ (accounting for 26–75% of tumor cells); or 3+ (accounting for more than 75% of tumor cells). The results of SATB2 immunostaining were compared with the serial sections immunostained with CK20 antibody.

Table I.- General data of patients.

Group	n	Age (<50:≥50)	Menstrual status (before menopause: after menopause)	Recurrence (yes: no)
Normal ovarian group	160	68:92	52:108	-
Mucinous cystadenocarcinoma group	53	23:30	15:38	18:35
Borderline mucinous cystadenocarcinoma group	55	21:34	16:39	17:38
Mucinous cystadenocarcinoma group	52	22:30	16:36	16:36
F value	-	13.728	17.917	15.728
P value	-	0.819	0.527	0.334

Statistical analysis

The accuracy binomial 95% confidence interval (CI) of each dye and double dye combination was used to calculate the sensitivity, specificity and correct overall percentage (in distinguishing mucinous tumors from mucinous ovarian tumors). Then, McNemar test was used to compare the sensitivity and specificity of the selected dyes directly. The exact P value was calculated. The 95%CI of the difference between sensitivity and specificity was calculated using the method based on the scoring interval described earlier. SAS/STAT software (Windows SAS system version 9.4, SAS Institute, Cary) was used for data analysis. Statistical significance was defined as $P < 0.05$.

RESULTS AND DISCUSSION*General data of patients*

One hundred and sixty patients with mucinous ovarian tumors were included in this study, including 53 cases (33.13%) of mucinous cystadenocarcinoma, 55 cases (34.37%) of borderline mucinous cystadenocarcinoma and 52 cases (32.50%) of mucinous cystadenocarcinoma. There was no difference in age, menstrual status and recurrence among the four groups of students ($P > 0.05$). Therefore, the influence of the above reasons on the experimental results was eliminated to make the data more comparable (Table I).

Diagnostic sensitivity and specificity of SATB2 and CK20 in mucinous ovarian tumors

The statistics of diagnostic sensitivity and specificity of SATB2 and CK20 in mucinous ovarian tumors showed that the diagnostic sensitivity, specificity and overall accuracy of SATB2 in mucinous ovarian tumors were 82%, 78% and 82%, respectively. The diagnostic sensitivity, specificity and overall accuracy of CK20 in mucinous ovarian tumors were 94%, 59% and 85%, respectively. The diagnostic sensitivity, specificity and overall accuracy of SATB2/CK20 in mucinous ovarian tumors were 65%, 99% and 89%, respectively. Compared with SATB2/CK20 single staining, SATB2/CK20 double staining had lower

sensitivity, higher specificity and higher overall accuracy (Table II).

Table II.- Diagnostic sensitivity and specificity of SATB 2 and CK20 in mucinous ovarian tumors.

Group	Sensitivity (95%CI)	Specificity (95%CI)	Overall accuracy rate (95%CI)
SATB2	0.82 (0.75-0.92)	0.78 (0.61-0.96)	0.82 (0.75-0.93)
CK20	0.94 (0.88-0.99)	0.59 (0.43-0.82)	0.85 (0.73-0.94)
SATB2 / CK20	0.65 (0.52-0.78)	0.99 (0.84-1.00)	0.89 (0.81-0.97)

Table III.- Correlation between SATB2 and CK20 expression levels and tumor pathological classification.

Group	n	SATB2	CK20
Normal ovarian group	160	0.61±0.18	0.35±0.13
Mucinous cystadenocarcinoma group	53	1.35±0.16	1.16±0.17
Borderline mucinous cystadenocarcinoma group	55	2.24±0.26	2.33±0.45
Mucinous cystadenocarcinoma group	52	3.15±0.37	3.26±0.47
F value	-	1833.023	1610.682
P value	-	<0.001	<0.001

Correlation between SATB2 and CK20 expression levels and tumor pathological classification

The association between SATB2 and CK20 expression levels and tumor pathological classification showed that compared with normal ovarian group, the expression levels of SATB2 and CK20 increased in the mucinous cystadenocarcinoma group, the borderline mucinous cystadenocarcinoma group and the mucinous cystadenocarcinoma group ($P < 0.05$). The expression of SATB2 and CK20 in the borderline mucinous cystadenocarcinoma group and the mucinous cystadenocarcinoma group was higher than that in the

mucinous cystadenocarcinoma group ($P<0.05$). Compared with the borderline mucinous cystadenocarcinoma group, the expression levels of SATB2 and CK20 in the mucinous cystadenocarcinoma group increased ($P<0.05$) (Table III).

Table IV.- Correlation between the expression levels of SATB2 and CK20 and the degree of tissue differentiation.

Group	n	SATB2	CK20
Poorly differentiated group	65	1.67±0.16	1.87±0.25
Moderately differentiated group	62	2.87±0.24	2.89±0.26
Highly differentiated group	33	3.58±0.43	3.87±0.35
F value	-	649.795	600.379
P value	-	<0.001	<0.001

Correlation between the expression levels of SATB2 and CK20 and the degree of tissue differentiation

The relationship between the expression levels of SATB2 and CK20 and the degree of tissue differentiation showed that the expression levels of SATB2 and CK20 in the moderately differentiated group and the well differentiated group were higher than those in the poorly differentiated group ($P<0.05$). Compared with the moderately differentiated group, the expression levels of SATB2 and CK20 in the highly differentiated group were higher ($P<0.05$) (Table IV).

Correlation between SATB2 and CK20 expression levels and prognostic outcome

The correlation between the expression levels of SATB2 and CK20 and prognostic outcome showed that the expression levels of SATB2 and CK20 in the general prognosis group and the good prognosis group were lower than those in the poor prognosis group ($P<0.05$). Compared with the general prognosis group, the expression levels of

SATB2 and CK20 in the good prognosis group decreased ($P<0.05$) (Table V).

Table V.- Correlation between SATB2 and CK20 expression levels and prognostic outcome.

Group	n	SATB2	CK20
Poor prognosis group	37	2.52±0.34	2.12±0.35
General prognosis group	56	1.63±0.21	1.28±0.23
Good prognosis group	67	0.87±0.12	0.67±0.09
F value	-	687.198	504.125

Multivariate analysis of SATB2 and CK20 expression levels in patients with mucinous ovarian tumors

The expression level of SATB2 and CK20 were not related to age, menstrual status tumor diameter ($P>0.05$), but related to recurrence, pathological typing, tissue differentiation, prognostic outcome, disease course and clinical stage ($P<0.05$) (Table VI).

DISCUSSION

Appendices and ovaries are the two main origins of mucinous tumors in pelvis or peritoneum. The distinction between these two origin sites can sometimes be very challenging, because mucinous tumors in either site are identical in morphology. Of all malignant appendiceal tumors, about 37% are mucinous cystic tumors, and women account for the majority of cases. Mucinous ovarian tumors account for 15% of all ovarian tumors, and most of them are unilateral (Gore *et al.*, 2019). Macroscopic, microscopic and immunohistochemical features are vitally important for the differential diagnosis of these tumors. In addition, pathologists may have few epithelium for diagnosis. If a set of immunohistochemical

Table VI.- Multivariate analysis of SATB2 and CK20 expression levels in patients with mucinous ovarian tumors.

Variable	Coefficient of regression	S.E.	Wald	OR	OR 95%CI	P value
Age	-1.829	0.378	3.819	0.816	0.284-1.738	0.179
Menstrual status	-2.839	0.536	4.819	0.738	0.162-1.839	0.718
Recurrence	-1.829	0.637	3.829	0.178	0.018-0.628	<0.001
Pathological typing	-3.728	0.583	5.839	0.839	0.178-1.893	<0.001
Tissue differentiation	-4.017	0.783	4.728	0.638	0.182-1.736	<0.001
Prognostic outcome	-5.816	0.638	3.526	0.976	0.244-2.624	<0.001
Tumor diameter	-2.527	0.157	3.725	0.782	1.354-1.937	0.627
Disease course	-3.825	0.678	4.987	0.983	0.224-2.937	<0.001
Clinical stage	-2.389	0.837	4.928	0.894	0.335-2.384	<0.001

staining is needed, tissue depletion will limit the number of staining that can be performed. Therefore, it is important to use immunohistochemical staining effectively to determine the origin site, without unnecessary staining to increase the hospital cost of patients (Van Treeck *et al.*, 2020). While many immunostaining or different combinations of immunostaining have been studied previously, including CK7, CK20, villin, CDX2, PAX8 and ER, the co-expression of mucinous ovarian tumors SATB2 and CK20 and its association with tumor pathological classification and prognostic outcome have not been reported.

SATB2 is a DNA binding protein, which participates in chromatin remodeling and gene regulation, and acts as a nuclear transcription factor. Among it, the physiological function of SATB2 involves growth and bone development. Especially, SATB2 is very important in the differentiation of cortical neurons and osteoblasts (Matsuo *et al.*, 2019). Therefore, SATB2 deficiency is related to some syndromes and non-syndromes of bone development, especially oral and facial fractures. At present, the role of SATB2 in the normal development of ovarian tumors remains to be determined. However, immunohistochemical analysis shows that SATB2 is positive not only in osteoblasts and cortical neurons, but also in epithelial lineage cells. Interestingly, in cells of epithelial lineage, the immunoreactivity of SATB2 is mainly limited to the lower digestive tract. In addition, some recent studies have shown that SATB2 is strongly expressed in most colorectal and appendiceal cancers (Han *et al.*, 2019). Therefore, SATB2 can be used as a useful marker in routine diagnosis to distinguish intestinal cancer of lower digestive tract (mainly colon and appendix) from other types of cancer. SATB2 is not expressed in normal ovarian epithelium (Hsu *et al.*, 2019). However, although SATB2 positive in mucinous ovarian tumors is very rare, SATB2 may be occasionally expressed in ovarian tumors. It is reported that 85% to 100% of CK20 metastatic from colon is positive and diffuse. Thus, it can be seen that this protein is widely used in differential diagnosis of primary and metastatic mucinous tumors (Harter *et al.*, 2019). Nevertheless, in 27% to 45% of cases, primary mucinous ovarian tumors may still express CK20 in focal or diffuse form (Panyavaranant *et al.*, 2019). Because of the overlapping expression patterns, immunohistochemical markers including CDX2, CK20 and CK7 cannot help to rule out ovarian metastasis from some gastrointestinal tumors (Kahn *et al.*, 2019). Our data showed that the diagnostic sensitivity, specificity and overall accuracy of SATB2 in mucinous ovarian tumors were 82%, 78% and 82%, respectively. The diagnostic sensitivity, specificity and overall accuracy of CK20 in mucinous ovarian tumors were 94%, 59% and 85%, respectively. The diagnostic

sensitivity, specificity and overall accuracy of SATB2/CK20 in mucinous ovarian tumors were 65%, 99% and 89%, respectively. Compared with SATB2/CK20 single staining, SATB2/CK20 double staining had lower sensitivity, higher specificity and higher overall accuracy. Compared with the normal ovarian group, the expression levels of SATB2 and CK20 in the mucinous cystadenocarcinoma group, the borderline mucinous cystadenocarcinoma group and the mucinous cystadenocarcinoma group increased in turn. The expression levels of SATB2 and CK20 increased in turn poor differentiation, medium differentiation and high differentiation. The expression levels of SATB2 and CK20 decreased poor prognosis, general prognosis and good prognosis in turn. Our data showed that the specificity of SATB2/CK20 double staining (all positive) in identifying ovarian mucinous tumors was significantly higher than that of SATB2/CK20 single staining.

To sum up, our results showed that the co-expression of SATB2 and CK20 could improve the sensitivity of ovarian mucinous tumors by immunohistochemistry. In addition, the co-expression of SATB2/CK20 was related to recurrence, pathological typing, tissue differentiation, prognostic outcome, disease course and clinical stage.

Statement of conflict of interest

The authors have declared no conflict of interests.

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